MP-470, a Rad51 Suppressor and Multiple TK Inhibitor, Retards Growth of Primary Human Glioblastoma Multiforma (GBM) Cells and Synergizes Effect of Temozolomide

Sarah Kamalek, Sabrina Liu, and Sanjeev Redkar
SuperGen Inc., Dublin, CA, USA

Abstract

MP-470 suppresses Rad51, essential for repair of DNA double-strand breaks, and multiple tyrosine kinases including mutant c-Kit, mutant FGFR1; mutant FLT3, and c-Met. In this study, primary GBM tumor specimens from eleven patients on standard care treatment prior to surgery were used to evaluate MP-470 efficacy as a single agent and in combination with Temozolomide. The GBM cells were tested for cell viability and plated in soft agar wells plates in a humidified incubator (37°C, 5% CO2), MP-470 was evaluated at 1.25, 2.5, 5, 10, and 25 µM and Temozolomide at 100, 200, 400, 800, and 1600 µg/mL in MTT assay and in soft agar plates using a colorimetric assay. After five days of incubation anchorage-independent growth was measured by Alamar Blue assay. Susceptibility to both drugs varied across the patients. MP-470 IC50 ranged from 0.05 to 29.6 µM (average 4.5 µM) and Temozolomide IC50 ranged from 146.5 to 715.4 µg/mL (average = 150.8 µg/mL). MP-470 was effective in all 11 tumor explants, Temozolomide demonstrated activity in 56 of the 11 explants. Furthermore, MP-470 was synergistic with Temozolomide in 4 of 11 explants; two combinations (MP-470 2.5 µM + Temozolomide) showed a synergistic effect on GBM cells. MP-470 inhibits growth of primary human GBM explants as a single agent and is synergistic with Temozolomide in the combination is more effective when MP-470 is first followed by Temozolomide.

Objective

- In this study primary GBM tumor specimens from eleven patients on standard of care treatment prior to surgery were used to evaluate MP-470 efficacy as a single agent and in combination with Temozolomide.

Materials & Methods

- Viable cryopreserved glioblastoma explants were used for this study.
- Tissues used in this study (Mosaic Laboratories, Lake Forest, CA) were collected from patients presenting for routine clinical evaluation in accordance with ethics guidelines. Viably cryopreserved glioblastoma explants were used for this study.
- The combination index (CI) was calculated using CalcuSyn (V2.0, Biosoft, Cambridge, United Kingdom) using the median-effect analysis defined by Chou and Talalay and the following equation:

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CI = \frac{D_1 \times D_2}{D_1 + D_2}
\]

where D1 and D2 are the doses of drug 1 and drug 2 that have x% effect when used in combination, and D1 and D2 are the doses of drug 1 and drug 2 that have the same x% effect when used alone.

Conclusions

- MP-470 demonstrated activity in all 11 glioblastoma explants tested.
- Temozolomide was effective in all 11 glioblastoma explants tested.
- MP-470 was effective in all 11 glioblastoma explants tested.
- Temozolomide synergized with MP-470 in 10 out of 11 explants.
- Temozolomide demonstrated complete resistance to temozolomide at all 5 concentrations tested.

References


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