ABSTRACT

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Phase I study of a novel glioblastoma radiation therapy schedule exploiting cell-state plasticity.

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BACKGROUND: Glioblastomas comprise heterogeneous cell populations with dynamic, bidirectional plasticity between treatment-resistant stem-like and treatment-sensitive differentiated states, with treatment influencing this process. However, current treatment protocols do not account for this plasticity. Previously, we generated a mathematical model based on preclinical experiments to describe this process and optimize a radiation therapy fractionation schedule that substantially increased survival relative to standard fractionation in a murine glioblastoma model.

METHODS: We developed statistical models to predict the survival benefit of interventions to glioblastoma patients based on the corresponding survival benefit in the mouse model used in our preclinical study. We applied our mathematical model of glioblastoma radiation response to optimize a radiation therapy fractionation schedule for patients undergoing re-irradiation for glioblastoma and developed a first-in-human trial (NCT03557372) to assess the feasibility and safety of administering our schedule.

RESULTS: Our statistical modeling predicted that the hazard ratio, when comparing our novel radiation schedule with a standard schedule, would be 0.74. Our mathematical modeling suggested that a practical, near optimal schedule for re-irradiation of recurrent glioblastoma patients was 3.96 Gy x 7 (1 fraction/day) followed by 1.0 Gy x 9 (3 fractions/day). Our optimized schedule was successfully administered to 14/14 (100%) patients.

CONCLUSIONS: A novel radiation therapy schedule based on mathematical modeling of cell-state plasticity is feasible and safe to administer to glioblastoma patients.

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