AZD1390 radio-sensitizes GBM by disrupting homology-directed DNA repair

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ABSTRACT

The ATM inhibitor AZD1390 disrupts cellular responses to ionizing radiation (IR) and is a potential radiosensitizer being tested in clinical trials. In this study, the effects of DNA radiosensitization and DNA repair pathways were evaluated in glioblastoma (GBM) cells and patient derived xenografts (PDXs).

AZD1390 (30 mg/kg) and higher sensitized (IR + GBM) mouse xenografts (PDXs) to IR. AZD1390-treated xenografts showed increased apoptotic body size and increased nuclear fragmentation as early as 1 hour post-IR compared to IR-alone xenografts. GBM lines showed similar effects. In addition, subcutaneous xenografts in mice treated with AZD1390 for 7 days and then exposed to IR showed a statistically significant increase in clonogenic survival relative to IR-alone xenografts.

The efficacy of AZD1390 in vitro was studied in xenografts, PDXs, and GBM cell lines. AZD1390 (10 μM) was found to be toxic to GBM cell lines, resulting in decreased DNA repair and increased sensitivity to IR in GBM cell lines. AZD1390 treatment resulted in a statistically significant increase in clonogenic survival relative to IR-alone xenografts in mice treated with AZD1390 for 7 days and then exposed to IR.

AZD1390 sensitizes GBM to IR in vitro. Western blotting showed that AZD1390 reduced p-HR and p-ATM levels. Cells treated with AZD1390 and IR exhibited increased p-HR and p-ATM levels compared to cells treated with IR-alone xenografts. The effect of AZD1390 on the ATM/p-HR pathway was confirmed by immunohistochemical analysis of xenografts from mice treated with AZD1390 and IR. AZD1390 treatment resulted in increased p-HR levels in xenografts from mice treated with AZD1390 and IR compared to IR-alone xenografts.

SUMMARY OF IN VIVO STUDIES

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