

2010

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Recommended Citation

Wachsberger, P.; Lawrence, R. Y.; Liu, Y.; Andersen, B.; and Dicker, A. P. (2010) "Effect of Cediranib, Temozolamide and Radiotherapy in U87 GBM wtEGFR and EGFRvIII-expressing Xenografts," *Bodine Journal*: Vol. 3 : Iss. 1 , Article 21. Available at: <http://jdc.jefferson.edu/bodinejournal/vol3/iss1/21>

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Effect of Cediranib, Temozolamide and Radiotherapy in U87 GBM wtEGFR and EGFRvIII-expressing Xenografts

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Introduction

Glioblastomas (GBM) frequently overexpress the epidermal growth factor receptor (wtEGFR) or its mutant, EGFRvIII contributing to radioresistance. New treatment strategies for GBM include blockade of EGFR signaling and angiogenesis. Cediranib (CD) is a highly potent VEGFR-2 RTKI that inhibits all three VEGF receptors. This study investigated the radiosensitizing potential of CD in combination with temozolamide (TMZ) in U87 GBM xenografts expressing wtEGFR or EGFRvIII.

Method

U87 GBM cells transfected with wtEGFR or EGFRvIII were injected into the hind limbs of nude mice. CD was dosed at 3 mg/kg daily (days 0-9); TMZ at 10 mg/kg on day 0. Radiotherapy (RT) consisted of 3 fractions of 5 Gy (days 0-2). VEGF was assayed from culture media 48 hr after treatment.

Results

In U87 EGFRvIII xenografts, RT, CD or TMZ alone significantly increased tumor doubling time (T_{2x}), when compared to control (4.6, 4.85 and 4.31 for CD, RT and TMZ respectively vs. 3.0 for control). TMZ + RT, but not CD + RT, was significantly better than RT alone ($T_{2x} = 6.22$ vs. 4.85 respectively). However, CD + TMZ was significantly better than TMZ alone ($T_{2x} = 6.3$ for cediranib + TMZ vs. 4.3 for TMZ). The triple combination of CD, TMZ and RT was significantly better than RT alone. In U87 wtEGFR xenografts, single agent RT and TMZ were significantly better than control ($T_{2x} = 7.84$ and 6.72 for RT and TMZ respectively vs. 3.45 for control). Single agent CD marginally increased T_{2x} compared to control (4.69 vs. 3.45, NS). CD + TMZ was significantly better than TMZ alone ($T_{2x} = 11.63$ vs. 6.72 respectively). The triple combination of CD, TMZ and RT was marginally better than RT alone but did not reach significance. In cell culture, TMZ, stimulated VEGF secretion from both U87 wtEGFR and U87 EGFRvIII cells; however, VEGF levels were higher from U87 EGFR cells than U87 EGFRvIII cells.

Conclusion

CD appears to be effective in GBM, both as a single agent and when combined with TMZ. Tumors expressing EGFRvIII were more sensitive than tumors expressing wtEGFR, possibly due to inability of CD to overcome excessive VEGF secretion by the latter.

Support: AstraZeneca Pharmaceuticals and the Radiation Therapy Oncology Group.