Enhanced efficacy of IGF1R inhibition in paediatric glioblastoma by combinatorial targeting of PDGFR\(\alpha\)/\(\beta\)


Source

Mol Cancer Ther. 2011 Jun 9. [Epub ahead of print]

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Abstract

Paediatric glioblastoma (pGBM), although rare, is one of the leading causes of cancer-related deaths in children, with tumours essentially refractory to existing treatments. We have identified IGF1R to be a potential therapeutic target in pGBM due to gene amplification and high levels of IGF2 expression in some tumour samples, as well as constitutive receptor activation in pGBM cell lines. In order to evaluate the therapeutic potential of strategies targeting the receptor, we have carried out in vitro and in vivo preclinical studies using the specific IGF1R inhibitor NVP-AEW541. A modest inhibitory effect was seen in vitro, with GI50 values of 5-6\(\mu\)M, and concurrent inhibition of receptor phosphorylation. Specific targeting of IGF1R with siRNA decreased cell viability, diminished downstream signalling through PI3-kinase and induced G1 arrest, effects mimicked by NVP-AEW541, both in the absence and presence of IGF2. Hallmarks of PI3-kinase inhibition were observed after treatment with NVP-AEW541 by expression profiling and Western blot analysis. Phospho-RTK arrays demonstrated phosphorylation of PDGFR\(\alpha\)/\(\beta\) in pGBM cells suggesting co-activation of an alternative RTK pathway. Treatment of KNS42 with the PDGFR inhibitor imatinib showed additional effects targeting the MAP-kinase pathway, and co-treatment of the PDGFR inhibitor imatinib with NVP-AEW541 resulted in a highly synergistic interaction in vitro, and increased efficacy after 14 days therapy in vivo compared with either agent alone. These data provide evidence that inhibition of IGF1R, in combination with other targeted agents, may be a useful and novel therapeutic strategy in pGBM.