Scottish Executive Health Department Chief Scientist Office

FOCUS ON RESEARCH

MITOCHONDRIAL POISONING AS A NOVEL STRATEGY TO OVERCOME RADIATION RESISTANCE OF GLIOBLASTOMA

Researchers

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Aim

The aim of the project was to develop and evaluate a novel treatment for GBM that combined ionising radiation with inhibitors of mitochondrial function either alone or in combination with anti-VEGF treatment.

Project Outline/Methodology

Using three different human primary GBM cell lines, we investigated the effects of mitochondrial poisoning, VEGF inhibition and irradiation in the 3D GBM stem cell model (Alvetex™ scaffolds) in both normoxic (20% O_2) and hypoxic conditions (1% O_2) as well as in conventional 2D cultures. Mitochondrial function was targeted using phenformin (complex I, AMPK inhibitor) and ME-344 (terminal respiratory chain complex inhibitor), while VEGF signalling was targeted using bevacizumab (anti-VEGF monoclonal antibody) and SU-5416 (small molecule VEGFR2 tyrosine kinase inhibitor). Active combinations identified *in vitro* were selected for *in vivo* evaluation in our well-characterised U87MGLuc intracranial model.

Key Results

This project generated encouraging pre-clinical data that strongly support two novel treatments for GBM: mitochondrial inhibition and Akt inhibition in combination with radiotherapy. In the case of mitochondrial inhibition, selection of an adequate inhibitor is crucial to achieve clinical efficacy: phenformin showed no activity in our in vitro assays and should not be evaluated in clinical trials for GBM patients, ME-344 exhibited cytotoxicity in vitro and in vivo, providing strong justification for the evaluation of ME-344 as single agent for infiltrative GBM in clinical trials.
The second treatment, Akt in combination with radiotherapy has also shown to be a promising alternative for the GBM in vitro, although in vivo data is still awaited.

Conclusions

ME-344 showed potent cytotoxicity against all GBM cell lines in both 2D and 3D condition, and demonstrated therapeutic efficacy as a single agent in U87MGLuc2 orthotopic xenografts by extending mouse survival compared to vehicle (Log Rank Mantel-Cox p=0.006).
Akt inhibition increased radiosensitisation of GBM cells 2D and 3D conditions. These results warrant further investigation into Akt and radiation for the treatment of GBM.

What does this study add to the field?

To the best of our knowledge, this is the first study identifying two novel therapies for GBM: mitochondrial inhibition and Akt inhibition in combination with radiation.

Implications for Practice or Policy

We predict that GBM patients that cannot be treated with surgery or radiation, such as those characterised by diffuse infiltration of the brain with neoplastic cells, or those with recurrent GBM would benefit from ME-344 treatment.

Where to next?

In order to move towards clinical trials, we will test ME-344 and Akt inhibition with the chemotherapy drug temozolomide, which is the standard treatment for patients with GBM. Using this approach, we aim to develop new treatment combinations that will improve tumour control rates and extend survival.

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