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Trial combining anti-cancer drug and radiotherapy may lead to treatment for brain tumor

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Results from a clinical trial of a new treatment for glioblastoma suggest that researchers may have found a new approach to treating this most aggressive of brain tumours, as well as a potential new biological marker than can predict the tumour's response to treatment.

Presenting the research to the 2013 European Cancer Congress (ECC2013) [1] today (Monday), Professor Wolfgang Wick will say that combining radiotherapy with an anti-cancer drug called APG101 – a fusion protein similar to an antibody – blocks a cell-signalling pathway called CD95 that plays a crucial role in the development of the cancer. "Blocking the CD95 system represents a new way of tackling glioblastoma – a cancer that has few available treatment options," he will say.

A total of 84 glioblastoma patients, who had already received initial treatment including radiotherapy and whose cancer had recurred, were randomised in the phase II clinical trial to receive either radiotherapy alone, or radiotherapy together with an intravenous dose of 400 mg of APG101 once a week [2]. Their average age was 57, and the trial was carried out between December 2009 and September 2011 in 25 centres in Germany, Austria and Russia.

Twenty-one percent of patients who were treated with the combination of radiotherapy and APG101 were still alive six months after treatment,

compared to four percent of those that were treated with radiotherapy alone. After two years, 22% of patients receiving the combination treatment were alive compared to seven percent of patients who did not receive it. The risk of death was reduced by 40% in the experimental treatment group, although this did not quite reach statistical significance.

Prof Wick, Chairman of the Neurooncology Programme at the National Centre for Tumour Diseases and Professor of Neurooncology at the University of Heidelberg (Germany) will tell the conference: "Glioblastoma is a very aggressive, fast-growing tumour that shows an infiltrative growth, making local therapies of very limited efficacy. The tumour is also resistant to all current chemotherapy treatments, and has devastating effects on the quality of life of patients. This brain tumour affects two to three people per 100,000, and is associated with a very poor prognosis, with an overall survival of 12 months.

"This is the first controlled trial of re-irradiation and the first performed in glioblastoma patients up to now. It was already known that APG101 might be an innovative approach for treating glioblastoma, but the size of the protein molecule was potentially too large to cross the protective blood–brain barrier and target the tumour. Radiotherapy opens up this barrier and may therefore be an effective vehicle for this compound."

APG101 plays a major role in the blocking of the CD95/CD95L system. CD95 is a protein that acts as a receptor on the surface of cells. When this cell receptor binds with the CD95 ligand (CD95L) – another protein – it prompts the cell to die.

"Until 2008, it was thought that activating this system represented a potential strategy for treating glioblastoma," Prof Wick will explain. "But then it was realised that this made the cancer cells resistant to cell death and actually increased their ability to proliferate and spread to other tissues. Therefore, inhibition rather than activation is now

considered a meaningful hypothesis to be tested, particularly in brain tumours."

The researchers found that patients with tumours expressing the CD95L protein had a worse prognosis than patients with tumours that did not express CD95L. However, CD95L-expressing tumours responded better to the APG101 combination treatment, with an overall survival of 11.5 months for these patients, compared to 8.2 months for patients without an active form of the protein.

"This also implies that CD95L would be one of the first predictive markers in neuro-oncology, which may help to define patients with glioblastoma deriving benefit from the new therapeutic strategy," Prof Wick will say. "At present, there is paucity of predictive markers that tell us how to treat patients in the glioma field."

Prof Wick and his colleagues are continuing their research: "We still need to improve our understanding of how APG101 is acting. We also envisage testing new combinations of APG101 and radiotherapy plus temozolomide, a chemotherapy drug used for treating glioblastoma. There is a need to explore the mode of action as well as the mode of acquired resistance to the compound in patients," he will conclude.

President of ECCO, Professor Cornelis van de Velde, commented: "Although these are preliminary results, they are very interesting because glioblastoma is such a fast-growing tumour and there are so few available treatment options for these patients. An improvement in the percentage of patients surviving for six months after being treated with the combination of radiotherapy and APG101 is significant. Furthermore, the discovery that CD95L is likely to be a predictive marker for patient response may help us to target treatments more effectively. The findings presented today are a further advance along the difficult path of finding a successful way to treat this aggressive cancer."

More information: [1] The 2013 European Cancer Congress is the 17th congress of the European CanCer Organisation (ECCO), the 38th congress of the European Society for Medical Oncology (ESMO) and the 32nd congress of European Society for Therapeutic Radiology and Oncology (ESTRO).

[2] Patients with recurrent glioblastomas after prior standard radiochemotherapy with temozolomide were considered for re-irradiation provided they had a tumour diameter of 1-4 cm and time since the end of prior radiotherapy was at least eight months.

[3] This study was sponsored by the company developing APG101, Apogenix GmbH in Heidelberg, Germany.

Abstract no: 3304, "A phase II, randomized, open-label, multi-center study of weekly APG101 + reirradiation versus reirradiation in the treatment of patients with recurrent glioblastoma". Central Nervous System proffered papers session, 09.00 hrs CEST, Monday 30 September, Hall 5.1.

Provided by ECCO-the European CanCer Organisation