Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

Detection of hypoxic regions in Oesophagogastric Carcinomas with 18F-fluoroazomycin-arabinofuranoside (FAZA) Positron Emission Tomography (PET) imaging

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Aim: 6 out 10 patients with oesophageal cancer (OC) die within a year of being diagnosed, indicating that use of current treatments needs to be optimised, and new more effective treatments developed. OCs often have low oxygen concentrations (hypoxia), which causes resistance to chemo- and radio-therapy and also drives the cells to proliferate and spread more rapidly. Detecting hypoxia would allow a more personalised and optimised use of current chemo- and radio-therapy, and kick start investigation of newer medicines – Hypoxia activated pro-drugs (HAPs) that are designed to specifically target hypoxic tumours cells. However, present methods for hypoxia detection are invasive, technically difficult and not suitable for clinical use - this has inhibited research progress. 18-F FAZA is a chemical that that is retained in hypoxic cells, and the retention can be detected by PET CT scanning. We aimed to validate the new non-invasive scanning technique 18 F FAZA PET CT which involves injecting patients with 18F FAZA, to detect hypoxia in OC- if validated this would accelerate development of more effective personalised approaches in OC involving current treatments and also new HAPs.

Project Outline / Methodology: To validate that FAZA PET CT detects hypoxic OCs, we aimed to correlate uptake of FAZA detected on PET CT scans in 20 patients with markers of hypoxia in their tumours removed at surgery .To provide information regarding how FAZA PET CT could be used to personalise the use of new HAPs , parallel laboratory experiments in cancer cell lines to investigate the unknown mechanisms by which FAZA is uptaken and retained in hypoxic cells.

Key Results: Unexpectedly, no FAZA uptake was seen in the tumours in 9 scans on the first 5 OC patients. Accordingly, before scanning further patients, we expanded our cancer cell line experiments to investigate these unexpected results. Cell line work demonstrated that expression of–Cytochrome p450 oxicdoreductase (POR) was essential for FAZA uptake and retention in hypoxic tumour cells. In hypoxia, POR catalyses reductive metabolism of FAZA to highly reactive metabolites which then bind avidly to large molecules thereby capturing the FAZA inside cells. We subsequently investigated POR expression in tumour tissues from 133 OC patients, and found that, POR expression was present in only 7.6% of hypoxic OCs - thereby explaining the lack of FAZA uptake seen on PET CT in OC patients. In contrast to our findings in OC, in a concomitant study we found FAZA uptake detectable by PET CT in colorectal cancers thereby validating the FAZA Pet scanning technique.

Conclusions: Our work demonstrates that 18 F FAZA PET is not useful to measure hypoxia in OC. We report the novel fining that tumour expression of POR is critical for FAZA retention in hypoxic tumour cells, and that expression of POR is rare in hypoxic OCs.

What does this study add to the field? Our results suggest that POR expression can be used as a low cost pre-screening test to determine which tumour types it is worthwhile investigating FAZA PET CT - thereby improving research efficiency in the future. Several HAPs, are known to be activated by POR in hypoxic tumour cells which allows targeting to these otherwise hard to treat cells. In other types of cancer, e.g. colorectal, FAZA PET CT could be used to non-invasively demonstrate POR expression in individual patient's tumours and so direct the personalised use of HAPs to those most likely to benefit.

Implications for Practice or Policy: Our results provide new information to accelerate development of methods to detect tumour hypoxia in patients.

Where to next: We are investigating POR expression in a wide variety of tumour types to direct future FAZA PET CT investigations. We are also investigating the role of POR in the activation of HAPs to evaluate the potential role of FAZA PET CT as a predictive test to personalise their use.

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