Markers of Proliferation

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Current status: FDG is by far the commonest used radiotracer in oncology nuclear medicine studies today. Cancer cells rely more on glycolysis for energy production than normal cells rather than oxidative phosphorylation, leading to increased uptake compared to background. The recently published PERCIST guidelines provide a reference standard for assessing FDG-metabolic response in tumours (1). Over recent years, there has been a large increase in the numbers of targeted agents which are being used in the clinic in oncology, which are often given in combination with conventional cytotoxic chemotherapy. This shift in treatment patterns demands more accurate readouts of tumour sensitivity and resistance than FDG, which may not be specific enough for some targets. The biological processes which are targets for novel imaging probes include: proliferation, angiogenesis and apoptosis, the probes can provide surrogate or direct readouts of these pathways. Test-retest studies are fundamental to the future success of these agents so that we can better define the criteria for treatment-related response. We will concentrate on [18F]FLT-PET studies of tumour cell proliferation.

Proliferation: Thymidine analogues are the basis for most PET probes of proliferation, with the majority of studies focusing on 3'-deoxy-3'-[18F]fluorothymidine (FLT), which is a substrate for thymidine kinase 1. Clinical studies have shown that it correlates with immunohistochemistry measurements of tumour proliferation in breast cancer, lung cancer (2, 3). Two reproducibility studies have shown that FLT uptake is reproducible in breast cancer and non-small cell lung cancer (4, 5). High background uptake is seen in the liver due to glucuronidation, and in the bone marrow due to physiological proliferation. Pilot studies suggest that the main area of utility for FLT-PET lies within response assessment, with encouraging results for measuring response to cytotoxic chemotherapy in breast cancer, brain tumours, gastric carcinoma, and in non-Hodgkin's lymphoma. Preclinical xenograft studies have shown FLT has a role to play in the evaluation of novel agents such as aurora kinase inhibitors, mTOR inhibitors, however clinical studies with have seen mixed results. EGFR inhibition with gefitinib suggests that FLT-PET responders have a longer time to progression than non-responders, whilst with erlotinib studies in non-small cell lung cancer have suggested that FLT response is related to progression free but not overall survival. FDG was thought more useful than FLT in terms of relationship to overall survival (6-8). Other nucleoside analogues for studies of proliferation (FMAU, BrDU) have been developed and will be covered in this session.

Conclusion: A new generation of imaging biomarkers are being developed to aid response assessment which should lead to more rapid drug development and improved outcomes for patients. Further large scale multi-centre studies are now necessary to determine their clinical utility in a general oncology population. Future developments may include multiplexing of radiotracers to quantify several biological processes at once thus providing individual molecular imaging biomaps for patients.

References