PET studies findings correlate with multi-drug resistant genes in the human gliomas

Takashi Tamiya MD; Daisuke Ogawa MD, PhD; Masaki Okada MD PhD; Keisuke Miyake MD PhD
[Institution]
Deaprtment of Neurological Surgery, Kagawa University Faculty of Medicine

Introduction

Molecular imaging modalities such as L-[methyl-11C]methionine (MET) positron emission tomography (PET), [18F]-fluoro-3'-deoxy-3'-l-fluorothymidine (FLT) PET, and [18F]-fluoromisonidazole (FMISO) PET have revealed intra-tumoral heterogeneity in the human gliomas. Especially, imaging hypoxia with FMISO PET may predict poor response to chemotherapy. The objective of this study was to evaluate the relationship between the high-uptake regions of MET, FLT, or FMISO and the expression of multi-drug resistant genes in the malignant gliomas.

Methods

Forty-one patients with gliomas (7 WHO grade II, 14 WHO grade III, 20 WHO grade IV) were investigated with MET, FLT and FMISO-PET studies. MET, FLT and FMISO uptake studies were combined with navigation system or stereotactic localization techniques and used as a guide for stepwise histopathological evaluation (Ki-67 labeling index) throughout the tumor space. In tumors with heterogeneous PET findings, the expressions of multi-drug resistant genes (MDR1, MRP1-5, ABCG2 and MGMT) were determined at high uptakes of some or all PET studies.

Results

All glioblastomas showed tumor uptake of MET, FLT, and FMISO. In all patients, the uptakes of each PET tracers showed intra-tumoral heterogeneity. Analysis of the histological correlation of tissue samples demonstrated the highest expression of Ki-67 labeling index within the high-uptake areas of all tracers. Overexpressions of MDR1 and ABCG2 were identified within the high-uptake areas of FLT and FMISO PET studies. The expressions of these genes were detected in the intra-tumoral microvessels and tumor cells. However, MRP 1-5 and MGMT were not influenced by these areas.

Discussion

1. The availability of a non-invasive imaging method (PET) which allows for measuring ABC transporter function or expression in vivo would be of great clinical use in that it could facilitate the identification of those patients that would benefit from treatment with ABC transporter modulating drugs.
2. Radiolabeled compounds used for brain imaging with PET must readily cross the BBB to reach their target. Efflux transpotters at the BBB-P-gp and BCRP could limit their uptake by the brain. The impact of BCRP and p-gp at the BBB on the transport of befloxatone and diprenorphine in vivo remains to be evaluated with PET

Conclusions

The maps of all PET uptakes strongly correlated with histopathology in malignant gliomas. Malignant foci can be accurately identified, and these findings have implications for prognostic evaluation and decision making for surgery and chemotherapy.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of PET studies 2) Discuss, the relationship between the high-uptake regions of MET, FLT, or FMISO and the expression of multi-drug resistant genes in the malignant gliomas.

References

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