Molecular Imaging with [123I]FIAU,[18F]FET and [18F]FDG for monitoring herpes simplex virus Type 1 Thymidine Kinase and Ganciclovir Prodrug Activation Gene Therapy of Cancer.

鄧文炳
Wang HE;Yu HM;Liu RS;Lin M;Juri G.G;Hwang JJ;Wei HJ;Deng WP*

Abstract

The ability to monitor tumor responses during prodrug activation gene therapy and other anticancer gene therapies is critical for their translation into clinical practice. Previously, we demonstrated the feasibility of noninvasive in vivo imaging with 131I-5-iodo-2'-fluoro-1-ß-D-arabinofuranosyluracil (131I-FIAU) for monitoring herpes simplex virus type 1 thymidine kinase (HSV1-tk) cancer gene expression in an experimental animal model. Here we tested the efficacy of SPECT with 123I-FIAU and PET with 5-18F-fluoro-2'-deoxyuridine (18F-FUdR), 2-18F-fluoroethyl-L-tyrosine (18F-FET), and 18F-FDG for monitoring tumor responses during prodrug activation gene therapy with HSV1-tk and ganciclovir (GCV). Methods: In the flanks of FVB/N female mice, 4 tumors per animal were established by subcutaneous injection of 1x105 cells of NG4TL4 sarcoma cells, HSV1-tk–transduced NG4TL4-STK cells, or a mixture of these cells in different proportions to model different efficacies of transfection and HSV1-tk gene expression levels in tumors. Ten days later, the animals were treated with GCV (10 mg/kg/d intraperitoneally) for 7 d. -Imaging with 123I-FIAU and PET with 18F-FUdR, 18F-FET, and 18F-FDG were performed before and after initiation of therapy with GCV in the same animal. Results: Before GCV treatment, no significant difference in weight and size was found in tumors that expressed different HSV1-tk levels, suggesting similar in vivo proliferation rates for NG4TL4 and NG4TL4-STK sarcomas. The accumulation of 123I-FIAU at 24 h after injection was directly proportional to the percentage of NG4TL4-STK cells in the tumors. The 123I-FIAU accumulation at 4 and 7 d of GCV therapy decreased significantly compared with pretreatment levels and was proportional to the percentage of HSV1-tk–positive tumor cells. Tumor uptake of 18F-FUdR in all HSV1-tk–expressing tumors also decreased significantly compared with pretreatment levels and was proportional to the percentage of HSV1-tk–positive tumor cells. The accumulation of 18F-FET decreased minimally

(about 1.5-fold) and 18F-FDG decreased only 2-fold after 7 d of GCV therapy, and the degree of reduction was proportional to the percentage of HSV1-tk–positive tumor cells. Conclusion: We have shown that -camera imaging with 123I-FIAU was the most reliable method for prediction of tumor response to GCV therapy, which was proportional to the magnitude of HSV1-tk expression in tumor tissue. 123I-FIAU imaging can be used to verify the efficacy of elimination of HSV1-tk–expressing cells by therapy with GCV. PET with 18F-FUdR reliably visualizes proliferating tumor tissue and is most suitable for the assessment of responses in tumors undergoing HSV1-tk plus GCV prodrug activation gene therapy. PET with 18F-FDG or 18F-FET can be used as additional "surrogate" biomarkers of the treatment response, although these radiotracers are less sensitive than 18F-FUdR for monitoring tumor responses to prodrug activation gene therapy with HSV1-tk and GCV in this sarcoma model