Non-invasive in vivo imaging with radiolabeled FIAU for monitoring cancer gene therapy using herpes simplex virus type 1 thymidine kinase and ganciclovir.

鄧文炳
Deng WP;Yang WK;Lai WF;Liu RS;Hwang JJ;Yang DM;Fu YK;Wang HE

摘要

An experimental cancer gene therapy model was employed to develop a non-invasive imaging procedure using radiolabelled 2'-fluoro-2'-deoxy-5-iodo-1-beta- d-arabinofuranosyluracil (FIAU) as an enzyme substrate for monitoring retroviral vector-mediated herpes simplex virus type 1 thymidine kinase gene (HSV1-tk) transgene expression. Iodine-131 labelled FIAU was prepared by a no-carrier-added (n.c.a.) synthesis process and lyophilised to give "hot kits". The labelling yield was over 95%, with a radiochemical purity of more than 98%. The stability of [(131)I]FIAU in the form of lyophilised powder (the hot kit) was much better than that in the normal saline solution. The shelf life of the final [(131)I]FIAU hot kit product is as long as 4 weeks. Cellular uptake of [(131)I]FIAU after different periods of storage was investigated in vitro with HSV1-tk-retroviral vector transduced NG4TL4-STK and parental non-transduced NG4TL4 murine sarcoma cell lines over an 8-h incubation period. The NG4TL4-STK cells accumulated more radioactivity than NG4TL4 cells in all conditions, and accumulation increased with time up to 8 h. The kinetic profile of the cellular uptake of n.c.a. [(131)I]FIAU formulated from the lyophilised hot kit or from the stock solution was qualitatively similar. For animal model cancer gene therapy studies, FVB/N mice were inoculated subcutaneously with the HSV1-tk(+) and tk(-) sarcoma cells into the flank to produce tumours. Biodistribution studies showed that tumour/blood ratios were 2, 3.5, 8.2 and 386.8 at 1, 4, 8 and 24 h post injection, respectively, for the HSV1-tk(+) tumours, and 0.5, 0.5, 0.7 and 5.4, respectively, for the HSV1-tk(-) tumours. Radiotracer clearance from blood was completed in 24 h and was bi-exponential. A significant difference in radioactivity accumulation was revealed among the HSV1-tk(+) tumours, the tk(-) tumours and other tissues. At 24 h p.i., higher activity retention was observed in HSV1-tk(+) tumours (9.67%+/-3.89%ID/g) than in HSV1-tk(-) tumours (0.48%+/-0.19%ID/g). After seven consecutive daily treatments with the prodrug ganciclovir, planar gamma camera imaging showed HSV1-tk(+) tumour regression at day 4, and complete tumour regression at day 7. These results clearly demonstrate that the simplified n.c.a. synthesis process developed in this study is reliable and that the [(131)I]FIAU product is useful for in vivo monitoring of HSV1-tk gene transfer, expression and gene therapy.