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Meeting Report | Molecular Targeting Probes - Radioactive & Nonradioactive

Synthesis and preclinical evaluation of a molecular probe for imaging lung cancer with L858R/T790M mutation of epidermal growth factor receptor (EGFR)

Muammar Fawwaz, Kenji Mishiroy, Ryuichi Nishii, Kazuhiro Shiba, Seigo Kinuya and Kazuma Ogawa

Journal of Nuclear Medicine May 2020, 61 (supplement 1) 471;

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Abstract

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Introduction: Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) have been widely used for treatment in non-small cell lung carcinoma (NSCLC). Although they have a great clinical effect, patients carrying the dual mutation EGFR^{L858R/T790M} only respond to third-generation EGFR-TKIs. Thus, detecting the mutation status of EGFR is essential before therapy to ensure effectiveness and efficiency. CO-1686 is one of the third-generation EGFR-TKIs, which are selective toward EGFR^{L858R/T790M} and so radiolabeled CO-1686 is expected to work in monitoring EGFR^{L858R/T790M} mutation. In this study, we aim to provide a novel radiolabeled probe, *N*-{3-[[2-[[4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl]amino]-5-(trifluoromethyl)pyrimidin-4-yl] amino]-5-([¹²⁵I]iodophenyl)acrylamide ([¹²⁵I]ICO1686) to determine the EGFR^{L858R/T790M} mutation for selection of sensitive patients to the therapy by imaging.

Methods: The precursor was synthesized by tributylstannylation of cold ICO1686. [¹²⁵I]ICO1686 was prepared by iododestannylation of a corresponding tributylstannyl precursor with [¹²⁵I]NaI and NCS. We evaluated the plasma stability and biological potency of [¹²⁵I]ICO1686 as molecular probes for detecting EGFR^{L858R/T790M} using three human NSCLC cell lines: H1975 (dual mutation EGFR^{L858R/T790M}), H3255 (EGFR^{L858R} active mutant), and H441 (wild-type EGFR). **Results:** A reliable [¹²⁵I]ICO1686 radiosynthesis

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May 1, 2020

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was established with high radiochemical yield (77%) and purity (>99%). In vitro radioactivity accumulation in H1975 was three and ten-fold higher than those in H3255 and H441, respectively. The cell uptake of [125 I]CO1686 into H1975 was significantly blocked with nonradioactive CO-1686, which indicates that the binding site of [125 I]CO1686 is identical with that of CO-1686. The tracer revealed high stability in plasma with >90% at 60 min. In vivo biodistribution study, the accumulation of the tracer in H1975 tumor (1.8 %ID/g) tended to be higher compared to that in H3255 tumor (1.6 %ID/g) at 60 min postinjection. However, the tumor-to-background ratio needs to optimize. **Conclusion:** This radiotracer holds great potential and can serve as a pioneer to discover new potential radiotracers for EGFR^{L858R/T790M} mutation.

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