Preparation and Evaluation of $^{177}$Lu Labeled Nitroimidazole Derivative for Targeting Tumor Hypoxia

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1. Introduction

Hypoxia has been known to be an important physiological parameter for tumor growth and has been reported to be the cause for poor response to chemotherapy. Mechanistically, tumor hypoxia results from an imbalance between oxygen delivery and oxygen consumption. The identification and quantification of tumor hypoxia may predict the outcome and may identify patients who might benefit from concomitant radiosensitizing therapy to overcome the hypoxia effect.

In nuclear medicine, there is an interesting observation that nitroimidazole derivatives can selectively accumulate in the hypoxic regions, a character of a good radiosensitizer.

In this study, we have synthesized a 2-nitroimidazole derivative containing a DOTA chelator by using a solid phase reaction. The nitroimidazole analogue was radiolabeled with $^{177}$Lu. Furthermore biodistribution study was performed to evaluate its tissue uptake, in vivo.

2. Methods and Results

All chemicals were purchased from Aldrich and used without any further purification. All the processes of the reaction were identified with NMR. $^{177}$LuCl$_3$ was produced by the KAERI (Korean Atomic Energy Research Institute).

2.1 Synthesis of 2-nitroimidazole-DOTA derivative

All procedures were done by using solid phase synthesizer. In order to prepare nitroimidazole-DOTA, we first designed and synthesized to introduce DOTA via selective deprotection of the protected lysine-Wang resin. After deprotection of the Fmoc using 20% piperidine, DOTA-Lys-Wang resin was coupled with 2-nitroimidazole and then Wang resin was eliminated under TFA:TIS:EDT:Thioanisole:water condition. Chemical purity was identified with HPLC that showed 2-nitroimidazole-DOTA derivative at 4.4 min. MS: $m/z$ 686[M+1]$^+$. 

2.2 Radiolabeling

For the radiolabeling, the solution vial was prepared containing 100ug of nitroimidazole-DOTA derivative, 5mg of ascorbic acid and 6mg of dihydroxybenzoic acid dissolved in 1M sodium acetate buffer (pH 5.5). After injecting radioisotope $^{177}$Lu (1mCi) to the vial, it was heated for 30min at 90℃ and cooled on ice. HPLC analysis was performed using the gradient system using 0.1% TFA in water(A), 0.1% TFA in ACN(B), Flow rate 1ml/min; 100-90% A in 2min, 90-60% A in 10min, 60-30% A in 2 min, 30-30% A in 3min, 30-100% A in 3 min. The HPLC analysis of the $^{177}$Lu-nitroimidazole-DOTA showed a single peak at 6.8min. (Fig.1).

2.3 Biodistribution study

Biodistribution study was performed on 18-23g female nu/nu Balb/C mice that had been subcutaneously implanted with the $1 \times 10^6$ Calu6 human lung cells. Tumors were allowed to grow for 21 d, at which time the animals receive 5uCi of $^{177}$Lu labeled nitroimidazole(1ug) in 100ul of saline via lateral tail vein injection. At specified time points (2, 24hr), the tumors, blood and various tissues and organs (heart, liver, spleen, kidney, stomach, small intestine, large intestine, lungs) were removed and weighed, and the
biodistribution was detected using gamma counter. The results show quick renal clearance.

![Biodistribution Results](image)

**Fig. 2.** Biodistribution results at 2 and 24h post-injection of $^{177}$Lu-labeled nitromidazole-DOTA.

3. Conclusions

We prepared a new nitroimidazole derivative containing DOTA as a chelating agent of a $^{177}$LuCl$_3$-precursor for the evaluation of the tumor targeting hypoxia. High radiolabeling efficiency was successfully performed under heating condition. Furthermore, $^{177}$Lu-labeled nitromidazole showed quick renal clearance as indicated by the high uptake in the kidneys.

REFERENCES


