総 説

アルファ線核医学治療のための薬剤開発の考察（その2）

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Discussion on Translational Research of Drug Product for Targeted Alpha Therapy — Part 2 —

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Summary

Regulatory science for translational research of targeted alpha therapy (TAT) drug product under international standard is very important now. We have recently published our report on safety evaluation standard for non-clinical studies which is essentially necessary for first-in-human TAT studies. Furthermore, we also focus on dosimetry in this report which objective is to guide the design and implementation of radiopharmaceutical therapy. Key to this is that absorbed dose estimates predict likely toxicity and tumor response to treatment. However, the dosimetry is especially challenging because of very short range and extremely high LET of alpha particles. It is not possible to administer a tracer level of activity in alpha-particle emitter therapy to obtain the pharmacokinetics required for dosimetry, therefore, preclinical microscale dosimetry studies must be combined with macroscopic whole-organ dosimetry.

Our report provides an overview of alpha-particle-emitting radiopharmaceuticals applied by micro-dosimetry developed by Johns Hopkins University. The micro-dosimetry study is applied on Ra-223 dichloride (Xofigo) which is the first alpha-emitter radiopharmaceutical that has received approval for the treatment of patients with castration-resistant prostate cancer metastasized to bone. It is implemented in a new clinical trial for treatment of patients with bone metastases in renal cell carcinoma. This approach is also illustrated for the immune checkpoint inhibitor, PD-L1 antibody to investigate as a means of alpha-particle emitter delivery in a combined immunological and alpha-particle emitter targeting strategy.

The newly proposed micro-dosimetric simulation is developed by Japan Atomic Energy Agency on the basis of PHITS coupled with -Stochastic Microdosimetric Kinetic (SMK) Model. This model will be established to adopt reliable extrapolation in preclinical studies for alpha-emitter radiopharmaceutical products as well as BNCT.

We propose our new evaluation system including ① biodistribution analysis by PET or SPECT imaging, ② localization analysis by auto-radiography for animal tissues using alpha-camera, ③ histopathological examination for delayed-type toxicities in preclinical animal studies. In this system, we expect ④ micro-dosimetric simulation in this report can provide how to think about safety and dose escalation and verification issues for development of new TAT drugs in advance.