5–11 Dual Treatment and Diagnosis Role Played by Simultaneous Emission of β- and γ-rays
— Production of Highly Purified Lutetium-177 for Radioimmunotherapy —

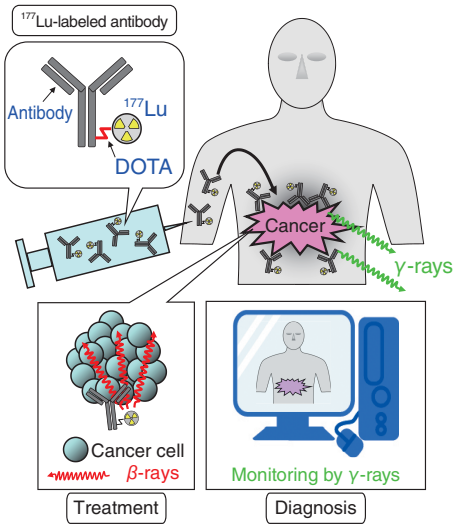

Fig.5-29 Treatment and diagnosis of cancer by a ^{177}Lu-labeled antibody
^{177}Lu is bound to an antibody through the chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The ^{177}Lu-labeled antibody administrated within the body binds to an antigen that is specifically expressed on a cancer cell. During treatment, β-rays emitted from ^{177}Lu kill the cancer cells. Simultaneously, diagnostic imaging to investigate the biodistribution in the body can be performed by measuring γ-rays from outside.

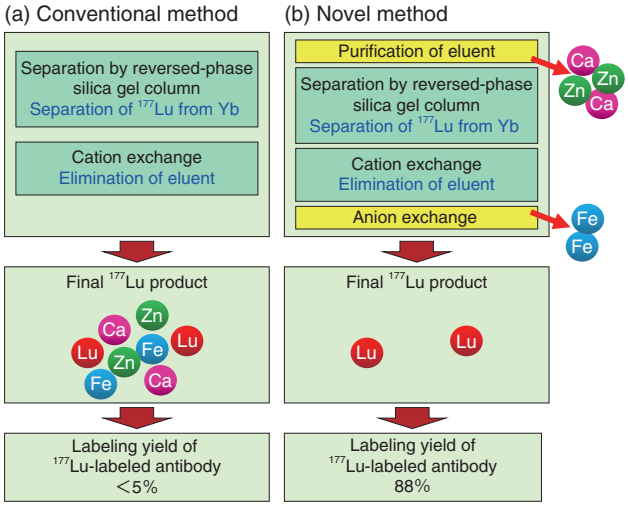

Fig.5-30 Separation of ^{177}Lu from neutron-irradiated Yb
In the conventional method (a) that we have developed, the labeling yield of the ^{177}Lu-labeled antibody was < 5%, owing to inhibition by Ca, Fe, and Zn included in final ^{177}Lu product. In the novel method (b), the Ca, Fe, and Zn were eliminated by both purification of eluent and addition of an anion exchange. Consequently, the labeling yield of the ^{177}Lu-labeled antibody increased up to 88%.

At present, beta-emitting radionuclides are used for cancer treatment. Lutetium-177 (^{177}Lu) is regarded as a promising novel radionuclide because it emits not only β-rays but also γ-rays. By measurement of the γ-rays from outside of the body, diagnostic imaging to investigate the biodistribution within the body can be performed (Fig.5-29).

Fig.5-29 shows a schematic diagram of radioimmunotherapy. ^{177}Lu is transported to a cancer cell by the antibody, which binds to an antigen that is specifically expressed on the cancer cell. By this therapy, if the purity of ^{177}Lu for the whole Lu isotope is low, the amount of ^{177}Lu transported to the cancer cell is reduced. Consequently, the therapeutic effect of ^{177}Lu upon the cancer cell is reduced. Two methods have been proposed to produce high purity ^{177}Lu. One is the direct method via the ^{176}Lu (n, γ) ^{177}Lu reaction. In this method, stable lutetium (^{176}Lu) is irradiated at reactors in Europe and America with large amounts of neutron-generation over a limited area. The other is the indirect method via the ^{176}Yb (n, γ) ^{177}Yb (half-life: 1.91 h) → ^{177}Lu reaction. In this method, stable ytterbium (^{176}Yb) is irradiated at reactors throughout the world with a low quantity of neutrons, and ^{177}Lu is separated from Yb. Therefore, to produce high-purity ^{177}Lu with the indirect method, various separation methods of ^{177}Lu from Yb have been investigated in many countries.

We have developed a method for completely separating ^{177}Lu from Yb using a reversed-phase silica gel column (Fig.5-30(a)) and have synthesized ^{177}Lu-labeled antibodies using the ^{177}Lu produced by our separation method. However, the labeling yield was < 5%. From the results of elemental analysis, it was found that calcium (Ca), iron (Fe), and zinc (Zn) were included in the final ^{177}Lu product, and that these metallic elements competitively inhibited the complexation between ^{177}Lu and 1,4,7,10-tetraazacyclododecane-1,4,7,10 -tetraacetic acid. Consequently, the labeling yield of ^{177}Lu-labeled antibody decreased. It was also found that these metallic elements were included as impurities in the regents of both 2-hydroxyisobutyric acid (2-HIBA) and 1-octanesulfonic-acid sodium salt (1-OS), eluents of the reversed-phase silica-gel column. Therefore, the eluents of 2-HIBA and 1-OS were purified by cation-exchange and chelating-ion-exchange columns in advance, respectively. Furthermore, an anion exchange was added as a final purification step (Fig.5-30(b)). The concentrations of Ca, Fe, and Zn in the final ^{177}Lu product were reduced from 87, 340, and 77 ppb to 13, 18, and 9 ppb, respectively, and the labeling yield of the ^{177}Lu-labeled antibody increased up to 88%. Consequently, we successfully produced highly purified ^{177}Lu capable of being applied to radioimmunotherapy.

If the highly purified ^{177}Lu can be produced using our method all over the world, radioimmunotherapy with ^{177}Lu will spread widely.

Reference

Watanabe, S. et al., Production of Highly Purified No-Carrier-Added ^{177}Lu for Radioimmunotherapy, Journal of Radioanalytical and Nuclear Chemistry, vol.303, issue 1, 2015, p.935-940.