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Radioconjugates based on the monoclonal antibody Nimotuzumab® for use in radioimmunotherapy.

Target-specific radiopharmaceuticals are becoming increasingly utilized in the management of cancer because they provide the unique tool for target-specific delivery of radionuclides to the diseased tissues. The encouraging results observed in the radioimmunotherapy of hematologic tumors have not yet been translated to solid tumors. The investigation of new radionuclides, new molecular constructs and better targeting strategies to prevent or overcome host toxicities will translate to progress in the therapy of solid tumors. For tumors associated antigens like EGFR, molecules that are overexpressed in tumors but are also expressed in normal tissues, monoclonal antibodies with intermediate affinity might have preferential uptake in target tissues overexpressing target antigen, while might decrease toxicity in normal tissue. In this work the preparation and preclinical evaluation of radioconjugates based on Nimotuzumab monoclonal antibodys with intermediate affinity and selected trivalent radiometals are described.

Nimotuzumab is radiolabeled with selected trivalent radiometals using bifunctional chelators. The cell-binding characteristics and toxicity of the radioimmunoconjugates was assessed using radioimmunoassay in cultured cell lines. Tumor targeting properties of Nimotuzumab labeled with 177Lu, 90Y and 188Re was evaluated in mice bearing human carcinomas xenografts with varying EGFR expression levels.

The radiolabeling procedures yielded a high and reproducible radiometal complexation suitable for the practical preparation of radiopharmaceuticals. Radioconjugates with high radiochemical purity and specific activity without significant loss in the targeting function were obtained. Radioimmunoconjugates showed higher cell growth inhibition in cultured cell lines (overexpressing EGFR or HER2) than unmodified monoclonal antibodies. Optimized preparation of Nimotuzumab labeled with n.c.a. 177Lu showed high stability in vivo. 177Lu-Nimotuzumab showed high specific tumor uptake accompanied by low uptake in normal tissues in mice bearing EGFR-overexpressing human epidermoid (A431) tumor xenografts. Preparation of radioimmunocojugate with 90Y and its preclinical evaluation is also described. The results using 188Re in a Fase I clinical trial are also included in the present investigation.

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