Bifunctional Chelators for Trastuzumab Conjugation and Successful Labeling with Radioisotopes

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Abstract

Bifunctional chelators (BFC) are molecules important for formulation of stable metal complex with targeting biomolecules such as antibodies, peptides or proteins. The chelators are covalently attached to the biomolecules on the one side and on the other coordinates to the radioisotopes.The goal are to produce a radiopharmaceuticals with pharmacokinetic and pharmacodynamic stability, without degradation of the complex in the physiological conditions and releasing of metal ion. The choice of the chelators depends of the type of radioactive isotope that will be used. Many efforts have been made in order to formulate a stable immunoconjugates of anti-HER2 monoclonal antibody trastuzumab with different types of BFC for further labeling with radioisotopes for imaging or radiotherapy of HER2 positive metastatic breast cancer. Succinimidyl-hydrazinonicotinamide (HYNIC) is important for trastuzumab conjugation and labeling with ^{99m}Tc and ^{188}Re. For formulation of radioimmunoconjugates with ^{212}Pb 1, 4, 7, 10-tetrakis (carbamoylmethyl)-1 , 4, 7, 10-tetraaza-cyclododecane(TCMC) have been used as a chelator. The most commonly used BFC are 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid (DOTA) and diethylene triaminepentaacetic acid (DTPA). Preclinical characterization was made of ^{111}In radiolabeled trastuzumab, previously conjugated with DTPA as a chelator. DTPA was used for trastuzuamab conjugation in a case of labeling with β emitters ^{86}Yand ^{90}Y. Chelating agent DOTA is significant for formulation of trastuzumab-radioimunoconjugates with gamma emitter ^{67}Ga, and potent therapeutic agents with β-emitter ^{177}Luand α emitter ^{225}Ac. The aim of our study is to formulate a stable immunoconjugates of trastuzumab with DTPA, DOTA and DTPA derivate 1B4M-DTPA (2-(4-isothiocyanatobenzyl)-6-methyl-diethylene-triaminepentaacetic acid) for further labeling with ^{90}Y and ^{177}Lu.

Keywords: Four to six keywords are to be provided for indexing purposes.