Pretargeting agents and ^{211}At-labeled effector molecules

Synthesis and preclinical evaluation for pretargeted alpha-radioimmunotherapy

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 8 juni 2012 kl 13:00.

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Avhandlingen är baserad på följande delarbeten:

I. Frost SHL, Jensen H, and Lindegren S
In vitro evaluation of avidin antibody pretargeting using ^{211}At-labeled and biotinylated poly-L-lysine as effector molecule
Cancer 2010; 116: 1101–10

II. Frost SHL, Bäck T, Chouin N, Jensen H, Hultborn R, Jacobsson L, and Lindegren S
In vivo distribution of avidin-conjugated MX35 and ^{211}At-labeled, biotinylated poly-L-lysine for pretargeted intraperitoneal α-radioimmunotherapy
Cancer Biother Radiopharm 2011; 26: 727–36

III. Frost SHL, Bäck T, Chouin N, Hultborn R, Jacobsson L, Elgqvist J, Jensen H, Albertsson P, and Lindegren S
Comparison of ^{211}At-PRIT and ^{211}At-RIT of ovarian microtumors in a nude mouse model
Submitted

IV. Frost SHL, Bäck T, Hultborn R, Jacobsson L, Jensen H, Albertsson P, and Lindegren S
In vivo distribution and tumor uptake of ^{211}At-labeled, biotinylated poly-L-lysine for systemic pretargeted radioimmunotherapy
Manuscript

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Pretargeting agents and ^{211}At-labeled effector molecules

Synthesis and preclinical evaluation for pretargeted alpha-radioimmunotherapy

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Abstract

Targeted therapies are treatment regimens in which tumor specific substances incorporating some sort of cell-killing effect are administered to patients. For cancer therapy they have emerged as a means of preventing metastatic relapse by reaching undetected microtumors, thereby improving survival rates. The key to all successful targeted therapy regimens lies in the specificity of the cell-killing effect, i.e. minimizing exposure to normal tissues while maximizing the response in malignant cells. Radioimmunotherapy (RIT) is a targeted treatment modality that utilizes tumor-specific radiolabeled antibodies for the delivery of ionizing radiation to tumors. Although a few RIT regimens have proven effective for certain types of cancer, success is generally limited by unfavorable pharmacokinetics. The large size of antibodies often leads to poor tumor penetration and slow clearance of unbound radioactivity, resulting in insufficient tumor-to-non-tumor absorbed dose ratios.

Pretargeted radioimmunotherapy (PRIT) offers a way of separating the slow targeting phase from the delivery of the radionuclide by using separate molecules for the two stages. In the first step, a modified antibody (pretargeting molecule) is administered and allowed enough time to localize at antigenic sites on tumor cells. Unbound pretargeting molecule is then cleared from the circulation, either spontaneously or with the aid of a clearing agent. Next, a small radiolabeled molecule (effector molecule) with high affinity for the pretargeting molecule is injected. The small size of the effector molecule enables both rapid accretion at pretargeted cells and efficient clearance of unbound radioactivity. With optimization of dosage and timing, very high tumor-to-non-tumor absorbed dose ratios can potentially be achieved using pretargeting.

Different radionuclides can be utilized in targeted therapies depending on their physical and chemical properties. Alpha particle emitters are well suited for irradiation of micrometastases because of their dense ionization and short range in tissue, thereby combining high cytotoxicity to targeted cells with low irradiation of normal tissues. Among the few available alpha-emitters, ^{211}At exhibits promising characteristics in terms of energy emission, decay chain, half-life (7.2 h), and labeling chemistry.

In this work, a pretargeting system utilizing the strong interaction between avidin and biotin was developed and evaluated to determine pharmacokinetics and therapeutic efficacy. Pretargeting molecules were produced by chemical conjugation of (strept)avidin and monoclonal antibodies, and effector molecules were based on biotinylated, charge modified, and ^{211}At-labeled poly-L-lysine. *In vivo* therapy studies in mice were performed using an intraperitoneal model of microscopic ovarian carcinoma, comparing the efficiencies of ^{211}At-PRIT and conventional ^{211}At-RIT. In addition, the pretargeting system was adapted for systemic administration and evaluated in a biodistribution study with mice carrying macroscopic subcutaneous tumors. Proof-of-concept was achieved, with efficient clearance and promising tumor-to-non-tumor absorbed dose ratios for the ^{211}At-labeled poly-L-lysine based effector molecule.

Keywords: Alpha particles, astatine-211, avidin, biotin, ovarian cancer, polylysine, pretargeted radioimmunotherapy

ISBN: 978-91-628-8469-7
E-publication: http://hdl.handle.net/2077/28957