

Development of targeted α therapy with Bi-213 and At-211 for the treatment of disseminated cancer

Synthesis and evaluation of pretargeting components and radioimmunoconjugates

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentlig försvaras i hörsal W. Sjölander, Medicinargatan 7, Göteborg onsdagen den 23 mars 2016 kl. 9.00

Av

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Avhandlingen är baserad på följande arbeten:

- I. Gustafsson AM, Bäck T, Elgqvist J, Jacobsson L, Hultborn R, Albertsson P, Morgenstern A, Bruchertseifer F, Jensen H, Lindegren S. *Comparison of therapeutic efficacy and biodistribution of ^{213}Bi - and ^{211}At -labeled monoclonal antibody MX35 in an ovarian cancer model.* Nuclear Medicine and Biology 2012; 1: 15-22.
- II. Gustafsson-Lutz A, Bäck T, Aneheim E, Albertsson P, Palm S, Morgenstern A, Bruchertseifer F, Lindegren S. *Therapeutic efficacy of α -radioimmunotherapy with different activity levels of ^{213}Bi -labeled monoclonal antibody MX35 in an ovarian cancer model.* Submitted
- III. Aneheim E, Gustafsson A, Albertsson P, Bäck T, Jensen H, Palm S, Svedhem S, Lindegren S. *Synthesis and Evaluation of Astatinated N-[2-(Maleimido)ethyl]-3-(trimethylstannyl)benzamide immunoconjugates.* Accepted for publication in Bioconjugate Chemistry, 2016
- IV. Gustafsson-Lutz A, Bäck T, Aneheim E, Palm S, Morgenstern A, Bruchertseifer F, Albertsson P, Lindegren S. *Biotinylated and chelated poly-L-lysine as effector for pretargeting in cancer therapy and imaging.* Submitted
- V. Gustafsson-Lutz A, Bäck T, Aneheim E, Albertsson P, Press OW, Hamlin D, Lindegren S. *Galactosylated, biotinylated and charge-modified polylysine: evaluation as clearing agent for pretargeting in cancer therapy and imaging* Manuscript



UNIVERSITY OF GOTHENBURG

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Synthesis and evaluation of pretargeting components and radioimmunoconjugates

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Radioimmunotherapy (RIT) is a type of targeted cancer therapy. The concept behind RIT is to deliver cytotoxic ionizing radiation to tumor cells by attaching radionuclides to tumor-specific antibodies. The radioimmunoconjugates identify and bind to tumor cells, isolated or in clusters, wherever located and possibly indistinguishable using imaging procedures. Thus, RIT is aimed to be an adjuvant treatment such as chemotherapy, but in contrast to chemotherapy specifically targeted to tumor cells, sparing healthy cells and tissues.

RIT can however have unfavorable pharmacokinetics when administered systemically. To circumvent this problem, pretargeted RIT (PRIT) can be applied. In PRIT, administration of the therapeutic agents is divided into several steps. A modified antibody (pretargeting molecule) is first administered, and is allowed enough time (several hours) to localize the tumor cells. The unbound pretargeting molecules are then cleared from the circulation, either spontaneously or by the guidance of a clearing agent. As a final step, a radiolabeled molecule (effector) is administered, which has high affinity for the pretargeting molecule. The small size of the effector results in both rapid accumulation at the tumor site and fast blood clearance of unbound radioactivity. Thus, a higher tumor-to-normal tissue dose ratio is achievable with PRIT than RIT.

Different radionuclides can be used for different purposes in targeted therapy. In the treatment of micrometastases, alpha-emitting radionuclides are well-suited because of their short path length and high linear energy transfer. These properties result in high relative biological effectiveness (RBE) as well as a reduced dependence of oxygenation and actively cycling cells when compared with low-LET radiation. When properly targeted, alpha-emitters have a high tumor-killing efficacy while sparing much of the normal healthy tissue due to their short range.

In this work, molecules for RIT utilizing the alpha-emitters ^{213}Bi and ^{211}At were produced and tested in vitro and in vivo. The principal evaluations of these molecules were focused on ovarian cancer therapy, utilizing a preclinical ovarian cancer mouse model. Results showed a therapeutic efficacy and a favorable biodistribution for the intraperitoneally injected alpha-RIT molecules. A new site-selective reagent for coupling ^{211}At to antibodies was also synthesized and evaluated. The resulting ^{211}At -labeled antibody conjugate showed good binding properties both in vitro and in vivo. Agents for PRIT were also synthesized, and exhibited promising properties for further preclinical evaluation in full PRIT systems.

Keywords: alpha particles, astatine, bismuth, MX35, ovarian cancer, polylysine, pretargeted radioimmunotherapy, radioimmunotherapy

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