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Review article

RADIOIMMUNOCONJUGATES OF VARIOUS MONOCLONAL ANTIBODIES AS POTENTIAL ANTICANCER THERAPY – REVIEW

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Abstract

Radioimmunoconjugates consists of a monoclonal antibody (mAb) linked to a radionuclide. Monoclonal antibodies (mAbs) are immunoglobulins able to recognize unique epitopes on a single antigen. MAbs therapy has emerged as a significant therapeutic choice for different types of cancer. When they contain a radioactive isotope for diagnostic or therapeutic purposes they belong to the group of radiopharmaceuticals. Radioisotopes are atoms that emit radiation and are used based on the type of radiation that is emitted. There are three types of radiation, alpha, beta, and gamma radiation. Alpha and beta radiation has a short range and are primarily used for radiotherapy purposes. Gamma radiation, on the other hand, has a wider range, is used for diagnostics, and can be detected using specialized detection systems.
To formulate a stable radiopharmaceutical, it is important to provide a stable link between the isotope and the carrier molecules (proteins, monoclonal antibodies, peptides, nanoparticles). The bifunctional chelators (BFC) contain a metal chelating group on one side and covalently binding to the biological molecules on the other side. Radioimmunoconjugates are the majority applied radiopharmaceuticals worldwide for diagnostic and therapeutic purposes and are composed of radioactive elements attached to the immune molecules, like monoclonal antibodies. Diagnostic radioimmunoconjugates can be used for body imaging and mostly for the identification of positive lesions and metastasis, while radiotherapeutics has shown efficacy in the treatment of solid tumors and hematologic malignancies.

Keywords: monoclonal antibodies, radioactive isotopes, bifunctional chelators, radioimmunoconjugates.

1. Development and structure of monoclonal antibodies

Antibodies are large Y-shaped proteins with a molecular weight of 150 kDa. They are composed of four polypeptide chains linked together by disulfide bonds: two light and two heavy chains. The heavy and the light chains have constant regions (c), which are identical to the same class of antibody, and unique variable regions (v), which contains antigen-binding region at the ends of the heavy and light chains. By enzymatic cleavage with papain, the antibody can be fragmented into two Fab and one Fc fragments. Fab fragments contain one variable region and one constant region. To be specific, the variable regions on Fab fragments contain three loops that are responsible for binding to the antigen, complementary determining regions - CDRs (CDR1, CDR2, CDR3). Fc fragment contains two constant regions and determines the antibody isotype (IgA, IgD, IgE, IgG, and IgM) and participates in the binding of effector cells and complement (Schroeder et al, 2010).

Human antibodies protect the body by two mechanisms: (I) direct binding and neutralization of the toxins and (II) activating of domestic immune response in two ways: complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) (Stern et al, 2005, Brekke et al, 2003).

A monoclonal antibody is a laboratory-produced protein that is engineered to attach specific cancer cells. The progress of genetic engineering over the years has provided many opportunities for the design and production of four main categories of monoclonal antibodies (pure murine, chimeric, humanized, and pure human) (Reichert et al, 2007). At first, pure murine antibodies were used, but they showed two major

disadvantages. Because hail from rodents they are recognized by the human immune system and leads to the development of human anti-murine antibodies (HAMA). HAMA inactivates and eliminates the murine antibodies and generates allergic reactions and anaphylactic shock, because of the formation of the antibody-HAMA complex. Murine Fc fragment provides a restricted binding to effector cells and activation of indirect pathways CDC and ADCC (Kricka, 1999). To overcome these problems and to minimize immunogenicity, the murine antibody was engineered and were obtained new antibodies like human antibodies, which provided a good pharmacological response [Stern et al, 2005, Hosono et al, 1992).

Chimeric antibodies are produced by cloning recombinant DNA containing the genes of the variable region of the murine antibody and the genes of the constant region of human antibodies (Morrison et al, 1984). These antibodies have over 65% of the human parts and have shown less immunogenicity in comparison with pure murine antibodies (Hosono et al, 1992). The humanized antibodies contain more than 90% of human protein sequences and are obtained by transplanting the CDR of the murine antibody into a human antibody. Because they have only 5-10% of murine proteins, humanized antibodies have shown the lowest immunogenicity (Riechmann et al, 1988). The nomenclature of the antibodies originates from the type of antibody. The suffix of the drug name can be: -momab (murine), -ximab (chimeric), -zumab (humanized) and –mumab (human) (Gerber et al, 2008).

2. Radioisotopes

Radioisotopes employed in nuclear medicine can be divided according to the application (diagnostic or therapeutics) and the method of production (generator, cyclotron, or reactor). Radionuclides which are gamma ray emitters are used as imaging agents (Radioimmunoimaging), using gamma cameras and single-photon emission tomography (SPECT) as imaging methods or radionuclides that are positron emitters using positron emission tomography (PET). Radionuclides that emit beta rays (electrons) or alfa emitters are used for therapy (Radioimmunotherapy - RIT) (Barbet et al, 2012).

The choice of appropriate radionuclide is critical for the efficiency of radioimmunotherapy. Alfa emitters should have a short range in tissue, which lead to good specificity and linear energy transfer, which makes them very cytotoxic and physical half-life which is relevant to carrier biological half-life. Considering all these criteria, a few α-emitters can be appropriate for RIT: 212Bi, 225Ac, 213Bi, 211At, and 223Ra (Larson et al, 2015, Imam et al, 2001). The advantage of these agents over beta and gamma radiation is that the inactivation of tumor cells is with few alfa particles, but on the other hand, alfa particles bind to their neighbor cells and irradiate them also. In some approved radiopharmaceuticals 223Ra dichloride is indicated for castration-resistant to prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease (Volkert et al, 1991).

131I or 90Y both are β- emitters approved from regulatory authorities, used for therapy for a long time, because of their emission characteristics, availability, and radiochemistry (Larson et al, 2015, Francoise et al, 2015). 131I is for treatment of thyroid-related diseases such as Graves' disease, solitary hyper-functioning nodule, and toxic multinodular goiter (Yeong et al, 2014). 131I and 90Y both also can emit γ-rays which make them useful as imaging agents (Schubiger et al, 2006). Another beta emitter is 89Sr used for painful bone metastases (Yeong et al, 2014). Under clinical trial are many beta emitters as 32P, 153Sm, 177Lu, and 188Re. Phase II clinical study of therapeutic effect of 177Lu labeled J591 have shown accurate tumor targeting, well toleration and reversible tumor suppression (Schubiger et al, 2006, Tagawa et al, 2013, Holland et al, 2010).

Several radiopharmaceuticals of 131I and 90Y used as therapeutics and diagnostic agents are approved. Another radioisotope from the group of radiometals taking part as an RIT agent is 67Cu which is a β-emitter, but its use is limited in contrast to 131I (Vivier et al, 2018).

Term molecular imaging can be precisely described as 'in vivo imaging of biological processes with

appropriate molecular probes' and is a powerful technique for diagnosis purposes (Holland et al, 2010). As methods for imaging are employed: radiotracers, gamma (γ)- camera (planar) scintigraphy, SPECT, and PET (Boswell et al, 2007). Radioisotopes produced from cyclotrons suitable for PET are 11C, 13N, 15O, and 18F. Unconventional radioisotopes produce from the generator for PET are 62Cu, 68Ga, 82Rb, 118Sb, and 122I (Holland et al, 2010). 89Zr is also a positron emitter that binds to mAbs and has been used for PET imaging (Poot et al, 2018).

Isotopes of Iodine used as imaging agents are 123I and 125I (gamma emitters) and 124I which is a positron emitter. 131I can be used for both SPECT imaging and RIT (Boswell et al, 2007). Besides its advantages and its spread use, 131I has prolonged γ-emission and need for patient isolation (Poot et al, 2018).

111In, a gamma ray emitting radionuclide, from the group of radiometals, is used for SPECT imaging (Vivier et al, 2018, Boswell et al, 2007). The use of 99mTc is widespread because of its production from the 99Mo generator. It is a gamma emitter agent used in SPECT imaging of prostate cancer, thrombus imaging, infection/inflammation imaging, and tumor imaging (Volkert et al, 1991, Holland et al, 2010, Liu et al, 1999).

Some of the antibodies used as radiopharmaceuticals may have direct interaction with radionuclides, which means don't need ligands for labeling, for ex. iodine and pertechnetate. For metalloradionuclides labeling is based on conjugation with most common bifunctional chelating compounds that may be linear as diethylenetriaminepentaacetic acid (EDTA), diethylenetriamine pentaacetic acid (DTPA) or macrocyclic as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), polyaminopoly carboxylic acids, etc. These bifunctional compounds interact with lysines or cysteine residues from proteins and form a covalent bond (Barbet et al, 2012, Vivier et al, 2018, Boswell et al, 2007).

For stabile complex formation, alfa radionuclide 212Bi is labeled with bifunctional chelates such as: DOTA or 1,4,7,11-tetraazacyclotetradecane-1,4,7,11-tetraacetic acid (Imam, 2001).

As chelators for 64Cu and 67Cu labeling are triethylenetetramine (TETA), bis-amino bis-thiol (BAT), DOTA, and DTPA. For the preparation of 111In labeled radioimmunocojugates with the desired uptake in targeted tissue and clearance from non-targeted issues, are used various chelators as DTPA-ε-lysine, DTPA, 2-(4-isothiocyanatobenzyl)-6-methyldiethylene-triaminepentaacetic acid (1B4M-DTPA), (R)-2-amino-3-(4aminophenyl) propyl]-trans-(S, S)-cyclohexane-1,2-diamine-pentaacetic acid (CHX-B-DTPA) and cyclic anhydride of DTPA (cDTPA) which develop different characters, also on their metabolism. The same chelators (DOTA, DTPA, 1B4M-DTPA) have proved to be successful in 90Y and 177Lu antibody labeling. [20]. Most successful chelators to produce 89Zr-mAbs, are iron-protected tetrafluorophenol-N-succinyldesferal (TFP-N-suc-DFO-Fe) or pisothiocyanatobenzyl-desferrioxamine B (DFO-Bz-NCS) (Poot et al, 2018).

As a ligand in 99mTc radiopharmaceuticals - 99mTc-sestamibi and 99mTc-bicisate are: 2-methoxy-2-methylpropylisonitrile (MIBI) and l,l-ethylene dicycteine diethyl ester, respectively (ECD). Another bifunctional ligand for 99mTc is hydrazinonicotinamide (HYNIC), which gives rapid and high yield radiolabeling (Liu et al, 1999).

68Ga labeling via ligand 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-D-Phe1-Tyr3-octreotide ([68Ga]-DOTA-TOC) shows higher detection rate of primary neuroendocrine tumors and related bone metastasis (Gabriel et al, 2007).

3. Radioimmunoconjugates for cancer treatement

The choice of antibody-based pharmaceuticals depends on the type of target antigens, expressed on the surface of the cells in hematologic malignancies and solid tumors. Commonly targeted tumor-associated antigens, located on the cancer cell surface, are: specific antigens on B cells - CD20, CD22 (CD – cluster of differentiation); prostate-specific membrane antigen (PSMA), mucin 1 (MUC1), carcinoembryonic antigen

(CEA), pancarcinoma antigen (TAG-72), human epidermal growth factor receptor (NER2/neu receptor), epidermal growth factor receptor (EGFR), tumor necrosis factor-related apoptosis-including ligand (TRAIL), epithelial cell adhesion molecule (Ep-CAM), Roundabout homolog 1 (ROBO1). Vascular endothelial growth factor (VEGF), unlike other receptors, is located on the surface of vascular endothelial cells and is responsible for the development of new blood vessels that feed the new cancer tissue (Boswell *et al*, 2007).

Radioimmunotherapy (RIT) has proven like effectiveness in hematologic malignancies. On the other side, solid tumors besides their restricted response, are attractive targets for RIT. The most of preclinical research has been focused on improving the clinical response and pharmacokinetics of radioimmunoconjugates in solid tumors at the same levels as hematologic malignancies. The uptake of mAb in solid tumors is obstructed by poor vascularization, poor lymphatic drainage, and from high interstitial pressure which is achieved in this type of tumor. The future goals in the field of radiopharmacy have been focused on developing radioimmunopharmaceuticals with improved therapeutic response, high localization in the target tissue, and decreased binding with normal tissue (Boswell *et al*, 2007, Jain *et al*, 2013, Palanca-Wessel *et al*, 2014).

In addition, are reviewed the FDA approved and commonly investigated RIT for diagnosis and treatment of different types of cancers.

3.1 Lymphoma

RIT is most developed in lymphomas, compared to other cancers. Radiolabeled tumor specific antibodies have shown efficacy in Non-Hodkin's lymphoma (NHL), especially against CD20 antigen. Two anti-CD20 radiolabeled IgG antibodies are FDA (Food and Drug Administration) approved for treatment of NHL, Zevalin® kit was approved in 2002 and contain an antibody (ibritumomab tiuksetin) and two isotopes 111In (for imaging) and 90Y (for therapy). One year later (2003), FDA had approved another good tolerated radiolabeled anti-CD20 antibody Bexxar® (131I-tositumomab) when is used as a first-line therapy (Mehren et al, 2003, Sharkey et al, 2006). Several radioimmunoconugates of first approved anti-CD20 antibody, rituximab, were tasted in the last two decades. The investigations of 131I-rituximab were advanced through phase I/II trials and have shown achievement of cumulative whole-body doses without significant hematologic toxicity (Illidge et al, 2009). In vitro studies have demonstrated successful formulation of stable kits with high stability and immunoreactivity (rituximab-DOTA and 1B4M-DTPA-rituximab) and satisfactory labeling with Lu-177 (Forrer et al, 2009, Gjorgieva-Ackova et al, 2014).

Many other antigens, located on B-lymphocyte, have been investigated as targets for therapy of NHL (CD21, CD22, CD52, CD30, CD37, CD80). In addition to anti-CD20, anti-CD22 antibodies are usually examined in the field of radiopharmacy. Radiolabeled anti-CD22 IgG antibody epratuzumab-DOTA with 131I and 90Y has shown significant success in the treatment of aggressive forms of NHL in patients who have failed chemotherapy (Bodet-Milin *et al*, 2013, Sharkey *et al*, 2003).

3.2 Colorectal and pancreatic cancer

In the last decades, significant achievements were made in the field of imaging and radiotherapy of colorectal (CRC) and prostate cancer (PC). CEA, as a specific and most studied solid tumor antigen, is highly expressed in epithelial cells in two already mentioned tumors. 131I and 90Y labeled labetuzumab (anti-CEA IgG) in an early I/II phase clinical trials for patients with CRC and PC have shown increased survival of treated patients versus control group (Boswell, 2007, Song et al, 2011, Goldenberg, 2007).

Different type of epithelial cancer cells, included CRC, are associated with EGFR overexpression. Cetuximab is already FDA approved anti-EGFR IgG1 monoclonal antibody for CRC and is used in a

various clinical and preclinical trials for development of radiopharmaceuticals for imaging and radiotherapy. Conjugated cetuximab with p-SCN-Bn-DTPA and labeled with Indium-111 was a subject of preclinical examinations as a potential agent for diagnosis and imaging of colorectal carcinoma (Benedetto et al, 2017). The same antibody, labeled with α or β- isotopes (90Y, 131I, 177Lu, 231Bi), is attractive for many clinical investigations and formulation of potent RIT agents (Sihver et al, 2014).
PSMA is commonly overexpressed and highly studied antigen in prostate cancer. Anti-PSMA monoclonal antibody 5A10 conjugated with DOTA and labeled with 111In was used for examination of antibody bio-distribution and development of advanced imaging agents to detect prostate cancer cells (Vilhelmsson-Timmermand et al, 2015).

3.3 Breast and ovarian cancer

For the past few years, were made a series of clinical and preclinical trials of radioimmunoconjugates for the treatment and imaging of HER2-positive breast cancer. The mostly investigated monoclonal antibody is FDA approved (for breast cancer) anti-HER2 trastuzumab. 111In labeling of anti-HER2 monoclonal antibody trastuzumab was done via two different chelators DTPA and DOTA. Both agents have proven to be valuable in PET/CT imaging (Hooge *et al,* 2004, Chan *et al*, 2011). 99mTc labeled trastuzumab via HYNIC is effective for the identification of HER2-positive lesions using gamma imaging (Chen *et al*, 2008). Two isotopes of gallium (67Ga and 64Ga) were used for the production of stable radioimmunoconjugates of DOTA-trastuzumab, as a potent drug for PET/SPECT molecular imaging and diagnosis of breast cancer (Alirezapour *et al*, 2013, Tamura *et al*, 2010). The obtained stable conjugate of trastuzumab labeled with β--emitter 177Lu via DOTA was subject to preclinical and clinical investigations in mice with breast tumors. The examinations have shown that 177Lu-DOTA-trastuzumab can be a new promising drug in the treatment of human HER2-positive breast cancer (Rasaneh *et al*, 2012, Ray *et al*, 2012). Potent alpha emitters 227Th and 225Ac were used for trastuzumab labeling. These studies suggest that both radioimmunoconjugates may be potent therapeutic agents against metastatic breast cancer with high HER2 expression (Heyerdahl *et al*, 2012, Ballangrud et al, 2004).
HER2 overexpression has been reported in ovarian cancer too. This is the reason why many radioimmunoconjugates with anti-HER2 monoclonal antibody trastuzumab were included in ovarian cancer examinations.
Already mentioned radioimmunoconjugate, 227Th-DOTA-*p*-benzyl-trastuzumab, has shown sufficient accumulation of radiation in tumor tissue with acceptable toxicity in ovarian cancer xenografts in mice (Heyerdahl *et al*, 2012). β+ emitter 86Y (86Y-DTPA-trastuzumab) was used for preclinical biodistribution and pharmacokinetics in mice with HER2-positive ovarian cancer. It was shown a selective uptake of the conjugate by the tumor cells and minimal localization in healthy organs (Palm *et al*, 2003). A nude mouse model with HER2-positive ovarian cancer was developed to investigate the immunoreactivity, internalization, and cytotoxicity of the conjugate 225Ac-trastuzumab. Studies have shown rapid internalization and cytotoxicity in cancer cells which leads to extending survival and low toxicity (Borchardt *et al*, 2003).

3.4 Lung, brain, and renal cancer

ROBO1 is a membrane protein overexpressed in small cell lung cancer (SCLC) and contributes to process of tumor metastasis and angiogenesis. 90Y labeled anti-ROBO1 IgG monoclonal antibodies have shown significant antitumor effect and have reduced tumor volume in SCLC mice xenografts (Fujiwara et al, 2015). It was found that some types of lung cancer and glioblastomas (brain cancer) have EGFR gene amplification and overexpression. Radiolabeled anti-EGFR monoclonal antibody cetuximab with diagnostic tracers proved to be a good candidate for PET imaging of EGFR positive lung cancer, while therapeutic

radionuclide-labeled cetuximab have showed a reduction in tumor size during the examinations (Sihver et al, 2014).
Anti-EGFR monoclonal antibody labeled with 123I have been using for brain glioblastomas scanning in a last three decades. Labeling the same monoclonal antibody with β- emitter 131I have shown good localization and improvement in neurologic parameters in relapsed patients with brain glioma (Kalofonos et al, 1989).
Monoclonal antibody G250 targets antigen G250 which is overexpressed in renal cell carcinoma (RCC). This antibody was used in various studies labeled with three isotopes (111In, 131I and 177Lu). Excellent images were obtained, with easy identification of positive lesions and metastasis of G250 positive RCC. The therapeutic properties of labeled G250 antibodies were exanimated in nude mice with human RCC xenografts. The in vivo studies have shown improved survival and reduced tumor growth after the administration of radiolabeled monoclonal antibody (Stillebroer et al, 2007).

4. Conclusion

The concept of personalized medicine has been growing over the past decades. Monoclonal antibodies (mAbs) undoubtedly play an important role in the transition from conventional medical practice to a more adaptive approach, to deliver the best therapy with the highest safety margin to a particular patient. The use of radiopharmaceuticals based on monoclonal antibodies is on the rise at various stages of preclinical and clinical trials. This includes a new approach to the use of radioimmunoconjugates of various monoclonal antibodies and radioactive isotopes with more appropriate characteristics. They represent a step forward in the development of the diagnosis and treatment of various cancers and other disorders through continuous innovation in molecular engineering, accumulated extensive knowledge of target biology, understanding of the mechanism of therapeutic mAbs, and greater appreciation of tumor immunosuppressive pathways.
Based on the promising results, therapy with radioactive conjugates can be developed in combination with other drugs and in repeated courses of treatment, just as chemotherapy is used. A combination of all possible new developments, including combining all possible new developments, including new antibody specificities, pre-targeted methods, fractional injections and the use of alpha emitters to improve RIT efficacy in solid radio-resistant tumors. Immuno-PET could help select patients for RIT, optimize injection activity, and monitor the effectiveness of non-invasive therapy.

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