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REVIEW

RADIONUCLIDES IN TARGETED THERAPY OF CANCER

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Radionuclides were first used for therapeutic purposes almost 100 years ago following the observation by Pierre Curie that radium sources brought into contact with the skin produced burns. For some malignant diseases, it is useful to destroy or weaken malfunctioning cells using radiation. The radioisotope that generates the radiation can be localised in the required organ. Cancer researchers, looking for an extremely potent and highly specific way to target cancer cells, are investigating the coupling suitable radionuclides to antibodies, antibody fragments or small peptides that bind cell surface receptors or other proteins specifically overexpressed by cancer cells. This is targeted radionuclide therapy. The targeted radionuclide therapy field is highly interdisciplinary and includes nuclear medicine physicians, clinical oncologists, surgeons, physicists, biologists, chemists and radiochemists. This review discusses the various strategies to improve the potential of cancer therapy through the development and application of innovative vectors labelled with several therapeutic radionuclides.

INTRODUCTION

About one-third of all patients admitted to hospitals are diagnosed or treated using radioisotopes. Over 10,000 hospitals worldwide use radioisotopes in medicine and about 90% of the procedures are for diagnosis. Most major hospitals have specific departments dedicated to radiation medicine. The most common radioisotope used in diagnosis is Tc-99m, with some 30 million procedures per year, accounting for 80% of all nuclear medicine procedures worldwide.[1] Rapidly dividing cells are particularly sensitive to damage by radiation. For this reason, some cancerous growths can be controlled or eliminated by irradiating the area containing the growth.[2] In developed countries (26% of world population) the frequency of diagnostic nuclear medicine is 1.9% per year[1] and the frequency of therapy with radioisotopes is about one tenth of this.

Internal radionuclide therapy is by administering or planting a small radiation source, usually a gamma or beta emitter, in the target area. I-131 is commonly used to treat thyroid cancer, probably the most successful kind of cancer treatment. Ir-192 implants are used especially in the head and breast. They are produced in wire form and are introduced through a catheter to the target area. After administering the correct dose, the implant wire is removed to shielded storage.

The use of permanent implants with I-125 or Pd-103 for the treatment of the prostate malign tumors in their incipient phases had become an usual medical procedure in the last 15 years. It is estimated that all over the world, more than 50,000 patients are yearly treated by this technique and it is expected to be increased in the near future.[3]

Many therapeutic procedures are palliative, usually to relieve pain. For instance, Sr-89[4] and Sm-153[5] are used for the relief of cancer-induced

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bone pain. Re-186 is a newer product for this.[6] While cancers with single bone metastatic site may be treated with external beam therapy, multiple sites imply the use of a radioactive agent that can distribute as a bone seeker.

The concept of targeted radionuclide therapy (TRT) appeared in 1898, when Paul Erlich started the concept of the "magic bullet" by using an antibody that recognizes antigenes associated to the tumor, as vector of a radionuclide cytotoxic, with the final aim of targeting and distroying the cancer cells. The first treatment of cancer by TRT was performed by William H. Beierwaltes[7] in 1951. However, experimentation on this approach really started in 1981 with polyclonal antibodies.[8,9] Research on TRT became more and more active over the last years using radiolabelled monoclonal antibodies (mAbs).[10]

TRT is a new kind of cancer treatment. It combines new developments in molecular biology and in radionuclides, which are new for medical applications.[11] The aim of this treatment is to obtain radiopharmaceutic products meant for the targeted distruction of the tumoral cells, by protecting the surrounding normal tissue. These products have high affinity for certain types of tumors. The tumor response depends on numerous variables, the most important being represented by the released cumulative dose, the rate of the dose, the tumor penetration and radiosensitivity. To an increase by 0.001% – 0.01% of the radiopharmaceutical injected dose per gram of tumor a cumulative dose is being released in the tumor tissue <1500 cGy, which represents less than the 5000 cGy necessary to obtain the therapeutic reply in most of the tumors treated with external radiation.[12-14] When the tumor growth is limited, the necessary dose to obtain a therapeutic answer cannot be achieved due to the limited doses of the risk organs (mainly the bone marrow with a limited dose of 150–200 cGy).[15]

TRT depends on three factors: the radionuclide, the transporter and the tumor target. The typical radiopharmaceutic product or radio-immunoconjugate contains a radionuclide, a tumor selective carrier molecule (monoclonal antibodies, antibody fragments, peptides, etc.) and a chelator linking the two (Fig. 1).

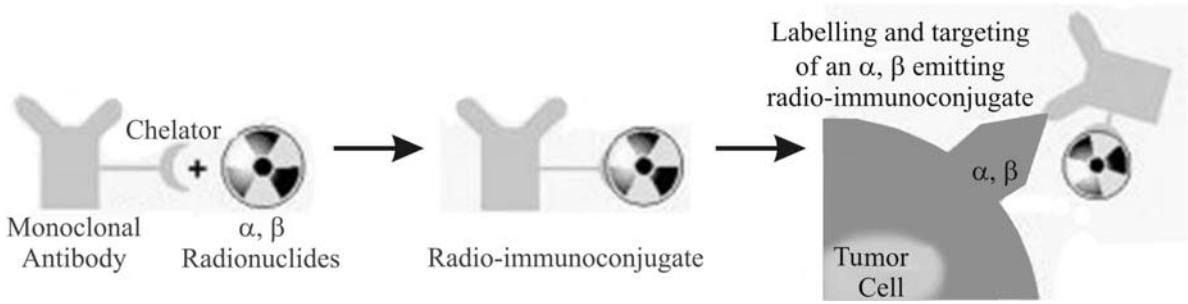

Fig. 1 – Radiopharmaceutic product.

Some biomolecules, like monoclonal antibodies, antibody fragments, small peptides, liposomes, dextrans, microspheres are tumor selective carrier molecules or transporters. These molecules can selectively target particular cancer cells and very interesting is the fact that they will find these cells, even if spread around the body and bind to them. If a beta- or alpha-emitting radionuclide is attached to such a tumor specific carrier, the beta or alpha particle produced during its radioactive decay can kill one or a few targeted cancer cells along its trajectory.[16] The principle strategy to improve cancer selectivity is to couple therapeutic agents to tumor targeting vectors. In targeted radionuclide therapy, the cytotoxic portion of the conjugates normally contains a therapeutic radiometal immobilised by a bifunctional chelator.

An advantage of using radiation instead of chemotherapeutics as the cytotoxic agent is the so called "crossfire effect".[17] In radiation medicine, the "crossfire effect" means that nearby cancer cells may also feel the effects of the cancer killing radiation therapy like cancer cells. In TRT the "crossfire effect" is a theory that the radiation from the radioactive antibodies can have a dual purpose: they can kill the cancer cells to which they attach and may kill adjacent tumor cells as well.[18]

1. RADIONUCLIDES

Choice of appropriate radionuclide

The choice of the therapeutic radionuclide is governed by several specific considerations such as

clinical indication, physical properties (mode of decay, energy, abundance of the emissions and half time), range of tissue penetration, chemical properties and some production aspects (specific activity, availability at needed scale and cost). The half time of the therapeutic radionuclide must be as reduced as possible so as not to affect the health cells. The range of the penetration into tissue is a great determinant of the size of tumors to be potentially treated[19] (affects other considerations regarding the type of targeting ligand and delivery carrier for the parent radionuclide).

Recognition of the advantages and disadvantages of the available choices of the radionuclides is important since different strategies are required to maximize their potential.

The physical half-life of the radionuclide, as well as the biological half-life for tumor uptake, retention and elimination from normal tissues of the carrying vehicle must be considered for radionuclide selection.

In particular, radionuclide half-life considerations include retention time for antibody or another targeting agent such as a peptide in tumor, in order to deliver a dose commensurate with the fraction of injected activity that localizes to target tissue. Thus, with conventionally radiolabeled antibodies or peptides (i.e., injected radionuclide bound to targeting agent, the half-life must be long enough for tumor uptake as well as tumor irradiation during time of useful tumor to normal ratios). The lastest studies have shown the therapeutic potential of yttrium, rhenium, copper and some of lanthanides (lutetium, samarium, dysprosium and holmium). As example, I-131 (8 day $t_{1/2}$), Re-186 (3.7 day, $t_{1/2}$) and Y-90 (2.7 day $t_{1/2}$) are suitable for whole antibody pharmacokinetics, where maximum tumor uptake of intact antibodies requires 24-28h, best tumor retention can persist for several days.[20,21] Conversely Re-188 (17h $t_{1/2}$) would be more compatible with short-lived small molecule targeting.

Types of radionuclides

Types of emissions considered in TRT are beta particles (electrons emitted with a wide range of energies), alpha decay (He^{2+} particles are emitted) and low energy Auger electron emissions.[22] Beta particles have the longest range in tissue followed by alpha particles and Auger electrons. The range of beta particles is 0.2-12 mm and that of alpha particles, 40-100 μm. The range of Auger cascade electrons are just of the order of a few nanometres, essentially creating a localized irradiated area (sphere) around the decay site of the parent radionuclide.[23] While the particulate property of the radiation decay mode determines the therapeutic potential, gamma ray emission often associated with the radiation decay, provides the ability to image the biodistribution in vivo, thus indicating tumor localization and non-target uptake and retention.[24,25] Ideally, gamma-radiation should be of low abundance such that contribution to non-target organ indication is minimized.

The chosen radionuclide for TRT may be an isotope with simultaneous β^- and γ emission (offers both the possibility to obtain performing radiopharmaceuticals for the treatment of the malignant tumors, resistant to conventional treatments and the monitoring of the therapy) or an alpha-emitting radionuclide (allows the selective destruction of the cancer cells).

Beta-emitting radionuclides

When a radioactive atom decays, one or more of a number of particles are emitted. Beta particles act like small billiard balls, travelling only short distances in the body until hitting nearby cells and killing or damaging them. It is these particles that are mainly responsible for delivering radionuclide treatment. Since the radioactivity is constantly decaying, the success of a treatment is dependent on the amount of radioactivity that is taken up in a tumor and how long it remains localised.[26] TRT is in full development and the researchers aim to finding new radionuclides, with simultaneous β^- and γ emission, as these offer the possibility to both administer treatment and see the radiation that delivers the treatment *in vivo*.

A wide range of beta emitter energies of emission and half life are available for TRT (Table 1).

The best results seem to be those obtained by using Re-188 as radionuclide, since it is easily bound to the majority of the possible transporters. The therapeutic radionuclide Re-188 is a radionuclide obtained in a generator 188W/188Re, with the characteristics: $t_{1/2}$ = 17 hours, beta emission of 2,1 MeV and gamma emission of 0,155 MeV. The stable form of Re is ReO_4^-. In the studies about the markers are used species of oxo rhenium in different valence states of Re, resulted by chemical processing under specific radiopharmaceutical conditions.

Table 1

Selected beta-emitting radionuclides for targeted radionuclide tumor therapy

Beta-emitting isotopes	$t_{½}$	Path-length [mm]	Energy delivered [Mev]
Iodine-131	8.1 days	0.8	0.6
Yttrium-90	64 h	2.7	2.3
Rhenium-188	17 h	2.4	2.1
Copper-67	62 days	0.05-2.1	0.6
Lutetium-177	6.7 days	0.04-1.8	0.5

Lu-177 is an ideal therapeutic radioisotope.[27] This is prepared from Yb-176, which is irradiated to become Yb-177, which decays rapidly to Lu-177. Lu-177 is emitting low beta energy (500 keV), which decreases the side effects of the radiations and is producing a penetrating field for the tissue, fitted for small tumors. As a rule, the beta particles can penetrate the biological tissue on a deep of 0.5-12 mm, depending on the energy of the particle (inverse ratio). The half-time of 6,65 days, will assure the connecting of the radioisotope to the biological compounds.

Lu-177 is emitting gamma radiation (113 keV), which assure their use for imagistics (the treatment monitoring), as well as for radiotherapy. The low energy beta of Lu-177, combined with longer half-time and the high specificity makes this radionuclide to be ideal for TRT with high doses, for the solid tumor.[28]

At the international level, the Lu-177 is tested for about 30 clinical applications: colorectal cancer, bone metastasis, non-Hodgkin lymphoma and lung cancer.

Y-90 is used for treatment of cancer, particularly non-Hodgkin's lymphoma, and its more widespread use is envisaged. Lu-177 and Y-90 are becoming the main TRT agents.[29]

The beta particles have the longest range in tissue (0.2-12 mm). The high penetrating distance is important for the solid and heterogeneous tumors, which are often poorly vascularised.

Alpha-emitting radionuclides

There has been a significant interest in targeting alpha radiation for TRT over the past several years (Table 2).

Table 2

Selected alpha-emitting radionuclides for targeted radionuclide tumor therapy

Alpha-emitting isotopes	$t_{1/2}$	Path-length [μm]	Energy delivered [MeV]
Bismuth-213	46 min	84	6.0
Actinium-225	10 days	50-80	8
Astatine-211	7.2 h	60	6

The rate at which charged particles impart energy locally to a medium is known as the linear energy transfer, commonly abbreviated as LET. The alpha particles possess kinetic energies ranging between 4 MeV and 9 MeV. The corresponding speeds are between 1.4 and 2.1×10^9 cm/sec. They are much less than the speeds of beta particles in the same energy range. Because of their slower speeds, the alpha particles spend more time than beta particles in the vicinity of the atoms they pass and exert much larger impulses on the orbital electrons. The impulses are increased still more because their charge and the electrical forces they exert are twice as great as those of electrons. As a result, the rate at which alpha particles impart energy to the medium along their path is much greater than that of beta particles. LET increases at lower energies and speeds. In air, the ranges are 3.5 cm for an alpha particle and 415 cm for a beta particle. An alpha particle with energy of 5 MeV travels a distance of 44 μm in tissue, whereas a 1 MeV electron (beta particle) will travel a distance of 3350 μm.[30,31]

So, alpha particles have a high LET and short range in tissue: they release their high energy, and therefore create damage, over just a few cell diameters.[32] They can therefore destroy tumor cells with minimal damage to surrounding healthy tissue. Cell killing essentially results from ionisation and rupture of chemical bonds due to the transfer of the alpha particle's kinetic energy.[33]

Alpha emitters, that have been studied for antibody mediated tumor targeting include: Bi-213 ($t_{1/2}$=46 min) and Ac-225 ($t_{1/2}$=10 days). Because of its short half-life (46 min), Bi-213 must be produced at the place of utilisation. It is a daughter product of Ac-225 (10 days half-life). Ac-225 is currently obtained by extraction from Th-229.

Another radionuclide recovered from used nuclear fuel is Pb-212, with half-life of 10.6 hours, which can be attached to monoclonal antibodies for cancer treatment. Its decay chain includes the short-lived isotopes Bi-212 by beta decay, Po-212 by beta decay and Tl-208 by alpha decay of the bismuth, with further alpha and beta decays respectively to Pb-208, all over about an hour.

Pre-clinical research and clinical trials suffer from limited availability of alpha emitters worldwide. Only Institute of Transuranium Elements (ITU – Germany), Oak Ridge National Laboratory (ORNL – USA) and Institute for Physics and Power Engineering (IPPE – Russia) can currently produce those mainly used today (Bi-213, Ac-225) in reasonable quantity and of high enough quality and purity (Bi-213/Ac-225 generators – approx. 3.8 Ci Ac-225).

As these are short-lived radionuclides, applications have been mainly in dispersed cancers, leukemia, malignant melanoma, cystic glioma, brain tumors and Non-Hodgkins lymphoma. Satisfying the requirements of homogeneous targeting of alpha emitters is more difficult with solid tumors, which are often poorly vascularised and may be access-limited by high interstitial pressure due to poor lymphatic drainage.

An experimental development of Targeted Alpha Therapy is Boron Neutron Capture Therapy (BNCT) using boron-10 which concentrates in malignant tumors. The patient is then irradiated with thermal neutrons which are strongly absorbed by the boron, producing high-energy alpha particles which kill the cancer. This requires the patient to be brought to a nuclear reactor, rather than the radioisotopes being taken to the patient.

So, BNCT is a binary form of cancer radiation therapy which uses a B-10 containing compound, that preferentially concentrates in tumor sites. The tumor site is then irradiated by a neutron beam. The neutrons in the beam interact with the B-10 in the tumor to yield highly energetic $_2He^4$ and recoiling $_3Li^7$ nuclei along with γ-radiation and 2.4 MeV of kinetic energy, as can be seen from reaction (1).[34,35]

$$_5B^{10} + _0n^1 \longrightarrow [\,_5B^{11}\,] \longrightarrow {}_2He^4 + {}_3Li^7 + 2.4\ \text{MeV} + \text{gamma radiation} \qquad (1)$$

Both $_3Li^7$ and $_2He^4$ particles have a very short range (about one cellular diameter) and cause significant damage to the cell in which it is contained. In this way, damage is done to the tumor cell, while largely sparing the healthy tissue. It should be noted that boron atoms and neutrons are not cytotoxic on their own, but by combining the components they have the potential to be highly cytotoxic.

BNCT was proposed in 1936 by Locher[36] and the first clinical trials took place at Brookhaven National Laboratory (BNL) in the 1950s and early 1960s using boric acid and some of its derivatives as delivery agents. These simple chemical compounds had poor tumor retention and were nonselective.[37]

In 1994 a new BNCT treatment was conducted using the Brookhaven Medical Research Reactor. Among the hundreds of synthesized low-molecular weight boron-containing compounds, there are only two boron compounds that have been used in BNCT clinical trials. These two low molecular weight (LMW) boron delivery agents (administered intravenously) are sodium mercaptoundecahydro-*closo*-dodecaborate, called sodium borocaptate ($Na_2B_{12}H_{11}SH$) or BSH and second (*L*)-4-dihydroxy-borylphenylalanine, referred to as boronophenylalanine or BPA and these are currently in Phase I and Phase II clinical trials.[38,39]

BNCT has been used in Japan for head and neck cancers in 2009.[40] In 2011 the department of oncology at Helsinki University Central Hospital, has declared that BNCT treatment has been given to over 200 patients, with recurred head and neck cancer or malignant brain tumor. 76% of patients responded well to the treatment and 30% were still alive two years after treatment; although only one patient has survived 55 months.

2. TUMOR SELECTIVE CARRIER MOLECULES

The types of radionuclide carriers are categorized based on the disease topology and

tumor morphology and not based on the type of construct (for example liposome- or polymer- or antibody-based). The application of nanomaterials in biomedicine is increasing rapidly and offers excellent prospects for the development of new non-invasive strategies for the treatment of cancer. A diverse range of nanometer-sized objects can recognize cancer tissue, delivery of anti-cancer drugs and destroy the tumors by different therapeutic techniques.

For vascularised tumors, the liposomes with encapsulated radionuclides have been extensively studied.[41] Liposomes are closed shell structures defined by one or more bilayer membranes that enclose an aqueous interior. The membranes consist of amphiphilic phospholipids (double-tailed, single-headed molecules) that self-assemble in water.[42] Phospholipid bilayer membranes have a thickness of about 4 nm and liposomes may entrap thousands of water soluble molecules in their internal aqueous compartment.[43] Liver and spleen are common accumulation sites for liposomes. Jonasdottir *et al.*[44] have described a pretreatment with non radioactive liposomes, which may saturate the hepatic macrophages resulting in lower liver uptake of the subsequently administered radiolabeled liposomes. Soares *et al.*[45] have shown that liposomes containing Gd-159 remained physically stable after 8h of irradiation and presented a low release profile of its content in two different biological mediums.

Dextrans loaded with radionuclides (Re-188) have also been extensively studied for passive accumulation at the sites of vascularised tumors.[46] Dextrans are branched polysaccharides composed of glucose molecules joined into chains of varying lengths. Similarly to liposomes, dextran's size that is of a few nm determines their localization in the body that is commonly at the liver and spleen.

It has been shown that use of smaller size microspheres (ceramics, polymers, resins or glass) is effective into the hepatic tumor interstitium.[47] These microspheres are loaded with beta particle emitting radionuclides, such as Y-90 ($t_{1/2}$=2.67 days, E_{max}=2.28 MeV) and Re-186 ($t_{1/2}$=3.78 days, E_{max}=1.077 keV, maximum range of 6 mm in soft tissue) and are very good for radioembolization. Radioembolization combines embolization (intravascular deployment of particles – microspheres loaded with beta particle emitting radionuclides) and brachytherapy (local administration of radiotherapy), thereby allowing delivery of high doses of beta radiation specifically to the tumoral area in an attempt to overcome the problem of permanent radiation-induced damage to nontumoral liver parenchyma.[48]

Antibodies are a powerful tool for use in diagnosis and therapy of the tumor,[49] because they bind with high specificity and high affinity to a variety of molecules, notably proteins and peptides. Whole antibodies provide high target binding specificity but their use in rapid tumor targeting and in vivo imaging is limited by slow tissue penetration, long circulating half-lives and often undesirable functions.

The selection of monoclonal antibodies (mAbs) for the treatment depends on: antigenic expression, affinity, molecular weight and other biological parameters.[50] MAbs are immunoglobulin G type antibodies. Most of them have been isolated from mice and from hybrid cells. The actual trend is to convert mAbs that have a potential clinical benefit and are of murine origin in antibodies with structure and function similar to human immunoglobulin. For this purpose there are developing genetically engineering technologies, like chimerisation and humanization. In 1988, Greg Winter and his team[51] pioneered the techniques to humanize mAbs, removing the reactions that many mAbs caused in some patients. The descriptive terms "chimeric" and "humanized" monoclonal antibody have been used to reflect the combination of mouse and human DNA sources used in the recombinant process.[52]

The chimerical mAb contains a constant region of human origin and variable regions from mice. These mAbs have the ability to interact with human complement and to induce cell-mediated antibody-dependent cytotoxicity, with less immunogenicity than murine antibodies.

Several studies showed[53] that by using fragments of antibodies, more exactly small monovalent antibody fragments (noncovalent single-chain variable fragment – scFv), it can be improved the molecule concentration in the tumor and the tumor tissue / normal tissue ratio, but with an unacceptable renal toxicity, that contraindicate the dose escalating.

Bie *et al.*[54] have described the construction, screening and humanization of the scFv (termed HDM) against human hepatocellular carcinoma using phage display technology. HDM has binding specificity to hepatocellular carcinoma and is potentially effective in tumor imaging and therapeutics. To improve its antigen-binding avidity, they constructed the scFv dimers by

shorting the linkers to 3-5 amino acid residues in same orientation as their parental scFv and assayed their biological functions, anticipating good behavior in antibody-targeted immunotherapeutic and diagnostic applications.

Evaluation of these immunotargeting forms has indicated gains in tumor-to-normal tissue ratios, but limitations still exist in kidney and liver uptake as well as tumor retention.

3. CHELATORS

It is necessary that carrier molecules for targeted radionuclide tumor therapy to be radioactively labelled with beta or alpha emitters. Labelling is done via a chelator, which must have two specific sites, *i.e*. "bifunctional", one binding the radionuclide and the other to the biomolecule. To be appropriate, this labelling or coupling must be fast (compared to the half-life of the alpha emitter) and stable, including in physiological medium *in vitro* and *in vivo*, and it must occur in strict conditions that do not degrade the biomolecule (for instance at room temperature).

For a beta emitter, the labelling is usually done via a chelator like diethylene triamine pentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).[55-57] An excellent example of the application of this approach has been the recent success in the treatment of neuroendocrine tumors in which somatostatin type 2 receptors (SSTR2) are overexpressed. In many of these cancers, specific peptides such as DOTA-Tyr3-octreotide (DOTA-TOC) and DOTA-Tyr3-octreotate (DOTA-TATE) and other SSTR2 targeting peptides, coupled to beta-emitting radionuclides such as Y-90 and Lu-177, have induced meaningful responses in patients with neuroendocrine tumors.

Another example is the impact of bifunctional chelators on biological properties of (111)In-labelled cyclic peptide RGD dimer.[58] What is the peptide RGD dimer? In the last few years research has focused on developing RGD peptides (arginine-glycine-aspartate sequence) that could mimic cell adhesion proteins and bind to integrins. Besides gamma-radiation, which makes In-111 suitable for imaging, it emits both Auger and conversion electrons with a medium-to-short penetration range (0.02-10 μm and 200-500μm, respectively).[59] Thus, there were synthesized (111)In(DOTA-3P-RGD(2)), (111)In(DTPA-3P-RGD(2)) and (111)In(DTPA-Bn-3P-RGD(2)) as potential radiotracers.[60] In these compounds 3P-RGD(2) = PEG(4)-E[PEG(4)-c(RGDfK)](2); PEG(4) = 15-amino-4,7,10,13-tetraoxapentadecanoic acid) and (DTPA-Bn=2-(p-thioureidobenzyl)-diethyl-enetriaminepentaacetic acid).

The factor limiting use of the alpha-emitters, like Ac-225 or Bi-213 in TRT, is the lack of an acceptably stable chelate for in vivo applications. Chappell *et al.*[61] described the first reported bifunctional chelate for Ac-225, which has been evaluated for stability for in vivo applications: 2-(4-isothiocyanatobenzyl)-1,4,7,10,13,16-hexaaza-cyclohexadecane-1,4,7,10,13,16 hexaacetic acid (HEHA-NCS). This ligand was conjugated to three monoclonal antibodies, CC49, T101, and BL-3 with chelate-to-protein ratios between 1.4 and 2. The three conjugates were radiolabelled with Ac-225, and serum stability study of the [^{225}Ac]BL-3-HEHA conjugate was performed.

CONCLUSIONS

The use of the radionuclides in the field of oncological therapy represents one of the most promising advances in the medicine in the last years. TRT kills cancer cells by delivering a lethal dose of radiation. The radiation is usually attached to a "carrier" that selectively seeks out tumor cells. TRT offers the advantage of delivering high radiation doses to a specific target. TRT can deliver treatment systemically, attacking multiple sites throughout the body. The high penetrating distance of the beta particles (Re-188, Lu-177 and Y -90) is important for the solid and heterogeneous tumors, which are often poorly vascularised. Clearly, the efficiency of conventional, beta-emitting radionuclides to kill isolated cells is limited by the deposition of most of the beta particle energy far from the targeted cell. For diseases such as dispersed cancers and for residual disease, the use of alpha emitters that deliver large amounts of energy (several MeV) in an area of less than 100 μm has been proposed. The use of alpha particle-emitting radionuclides such as Ac-225 or Bi-213 or At-211 should allow to efficiently eradicating disseminated microscopic clusters of tumor cells or isolated tumor cells which fit well with the short path length of alpha particles. Finally, TRT is a relatively benign treatment that does not incur the side-effects, such as hair loss and prolonged nausea, often seen in more conventional treatments.

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