ejpmr, 2019,6(12), 551-559

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON APPLICATION OF RADIOISOTOPES IN CANCER THERAPY

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Article Received on 22/10/2019 **Article Revised on 11/11/2019** **Article Accepted on 02/12/2019**

ABSTRACT

Radiopharmaceutical basically deals with the application of radioactive nuclides as a therapeutic agent in different diseases treatment and somewhere also as sterilising agent. The therapeutic action depends on the radiation potential of nuclides which is utilised to terminate the cancerous cell by either implanting nuclides close to the tumour or by selective delivery of nuclides to the malignant cells using immunobiology. Radionuclides are outlined to be more lethal towards malignant cells in comparison to normal cells, and this stimulated the researchers to use radionuclides in cancer treatment. "**TELETHERAPY**" one of the method for treating deep settled tumours is through the application of a direct powerful narrow beam of gamma rays [ϒ], emitted by an artificial isotope, into the tumour. Cobalt-60 is most commonly used isotope for teletherapy. In **"BRACHYTHERAPY"** compact source of radiation is implanted for treatment of superficial tumours. The recent advancement in drug delivery stimulated the focus toward the application of monoclonal antibodies (mAb's) for selective targeting of the malignant cells. Previously the mAb's used were derived from mouse which is recently seen to form HAMA (Human Anti-Mouse Antibody). Genetically engineered and humanised mAb's appear to be one of the most promising strategies to avoid HAMA formation. This review include the detailed study and the recent application of radioisotopes like ^{90}Y, ^{212}Bi, ^{213}Bi,^{123} I & ^{124} I in treatment of cancer through radio immunotherapy.

KEYWORDS: Radiopharmaceuticals, Radionuclides, HAMA (Human Anti-Mouse Antibody), Radio immunotherapy, mAb's.

INTRODUCTION

Radiopharmaceutical are radioactive isotopes which are used to diagnose [to find the traces] or work as a cancer therapy. Radioactive isotopes have unstable nucleus that decays or emit excess radiation or energy until the nucleus becomes stable. To date, researchers have discovered radioactive substances that can target various cancer like thyroid cancer, lymphoma, ovarian cancer, brain cancer or cancer which widespread to the bones. In the thyroid cancer the cause is unknown or poorly understood but may involve the genetic and environmental factors. To treat the thyroid cancer patients undergo the medication, surgery and radiation therapy to kill the cancerous cell which left after the surgery. Radioactive substances administered in the different form such as orally [in form of pill], IV and interstitial [inserted into the cavity]. A radiopharmaceutical is a drug made up of radioactive substances i.e. radionuclide's. Sometimes it bound with the mAb which attaches to the cancerous cell. Examples of radioactive substances are Cobalt-60, Iodine, Bismuth, Radium, Strontium and Yttrium [Y]. Conventional malignant tumor medication exhibits an absence of specificity, poor solubility and distribution, unfavourable pharmacology and high tissue harm or toxicity. Targeted drug delivery systems like passive and active targeting nanocarriers, with diameters ranging from 10-100 nm are developed to enhance the biodistribution, medicine, therapeutic and toxicity properties of agents used in cancer diagnostics and therapeutics. Radiopharmaceuticals consist of two components, a targeting carrier and a trace amount of radionuclide with a specific radiation. The radionuclide radiation characteristics and selectivity or specificity of delivery systems determine the tumour therapeutic efficacy and diagnostic quality.[3,8,24]

Adavantages of Radioactive Isotopes In Cancer

- Identify the abnormalities early in the progression of the diseases.
- Give accurate result, if proper metabolic time and technique applied.
- Wide ranges of stable isotopes are available for cancer therapy.

- Immune reactions are highly specific and sensitivity when patient is treated over conventional.
- Easier and cheaper to dispose of lower doses.
- More reliable, easily administration and isolation procedure required.

Differences Between Stable And Radioactive Isotopes

Stable Isotopes	Radioactive Isotopes
Most abundantly found in nature.	Less abundantly found in nature.
No or less emission of radiation.	Spontaneous emission of radiation(α,β,Υ)
Atomic no. And mass are constant.	Constantly changing.
Detection by chemical spectroscopic.	Detection by external detectors like gas chambers/ scintillation.
Not hazards except toxic chemical	Deteriorate effects on biological tissues.
No special handling precautions.	Special handling precautions required.
No special application needed	Special application in research(mutagenesis), diagnosis(RIA)/ therapy (R_x of cancer)

Radionuclide To Treat Different Oncology

The effect of radiation on tissue was found deteriorate and radiation necrosis. Radiation has lethal effect against the uncontrolled proliferation of cancerous cell. Not only radiation inhibits the growth of cancer cell, but seemed to be more effective against them than against normal body cells. These captivate the interest of many researches to use radionuclide in cancer treatment. One method of treatment is to direct a narrow beam of radiation into the tumour from outside of the body. Back in the days radium needles was used about 1.55mm in diameter but hollow contain few mg of Radium-223 was pushed in tumour and left there for several days. The early teletherapy units in back 1920 have contained radium a naturally occurring radioactive element. But the radium teletherapy units were faced with a cruel dilemma: only few grams were available. 10 gm was considered as a large unit, yet this is equivalent to about 6 curies of cobalt-60 or about 24 curies of cesium-137. In contrast, modern cobalt holds in between 1000-5000curies. It was not a question of cost, but availability! Since large amount of radium didn't exist. The radium units had to be used with the source quite close to the surface of patient, usually 5-10 cm. However its intensity is one of the factors which create the problem, i.e. In order to treat malignant cells effectively, the source must be as far away from the patient as possible (50-100cm). But the radiation intensity decreases in proportion to the square of the distance. Radium units could thus be used only for treating tissues quite closer to the surface, and in spite of the short working distances, exposure times of 30 mins or longer for each irradiation were common. In the modern teletherapy units very large amounts of cobalt-60 & cesium-137 available through atomic reactors has completely transformed the situation, as already indicated. The gamma rays emitted by cobalt-60 are virtually mono-energetic, of an average 1.25MeV. Those for cesium-137 have energy 0.66MeV. The higher the energy of the cobalt gamma rays leads to the greater penetrating power of the beam. Radiation reaches deep lying tissues with less absorption in, and hence destroys the overlying tissues. This fact allows some simplification in treatment technique which can't be over emphasised. The main requirement of an isotope for use in teletherapy may thus be summarised as follows: i) it must have long half-life; ii) it must emit high energy gamma rays; iii)it must be available in large quantities, and iv) it must be available with specific activity so that radioactive element emitting a very high intensity of radiation can be concentrated in a source of small physical dimensions. For ex. Co-60 has 5.3 half-life & Cs-137 has 30 years of half-life. But the dosimetry problem arise, i.e. the determination of the dose of radiation. Radioisotopes are used as a source of radiation for cancer therapy. Several sources may be combined so that the resultant radiation field is matched to the shape and size of the tumour. This form of treatment known as brachytherapy or curie therapy, can delivered a well-defined dose to the tumour with minimum damage to the surrounding tissues: because of the properties of radioactive element and dose delivered with the intensity to the surface. Brach therapy implant is the most effective from of radiotherapy shown in figure 1.

TELETHERAPY EQUIPMENT FOR CANCER TREATMENT. A NARROW BEAM OF RADIATION DIRECTED DOWNWARDS TO PASS THROUGH THE TUMOUR. THE RADIATION SHIELD AT THE TOP CONTAIN RADIOACTIVE ELEMENT WHICH ROTATED ABOUT THE PATIENT SO THE BEAM ENTERS THE BODY FROM DIFFERENT DIRECTIONS.

FIG. 1: Brachy Therapy.

The recent advancement suggests the use of monoclonal antibodies (mAb). MAb can selectively target malignant cells in humans but lack in ability to destroy these cells by immunologic mechanism. Thus genetically engineered mAb labelled radionuclide's formed mAb carries the radionuclide to the tumour. MAb bind to the antigen on the tumour and allow deteriorating the cancerous cells shown in figure 2.

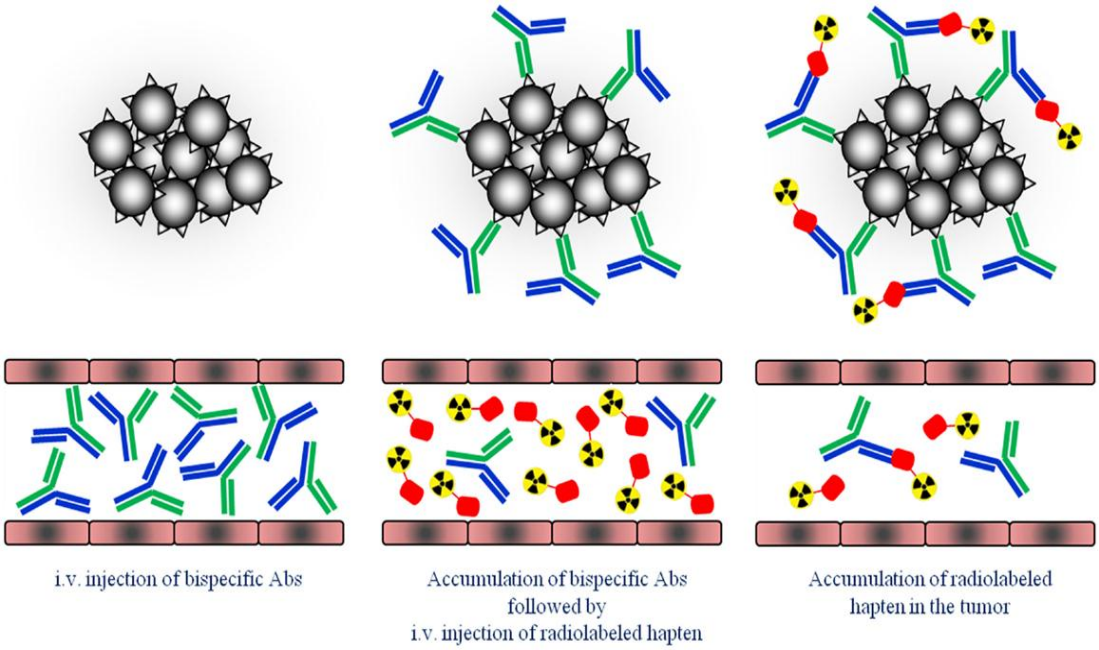


Fig. 2: Mechanism of MAb.

Cancer exhibits up-regulated cell growth, with an ability for tumour cells to invade and metastasize. A century ago, Paul Ehrlich hypothesized that a 'magic bullet' could be developed to selectively target cancer disease. Over the past few decades, the progress in molecular biology and the understanding of malignant transformation and tumour genesis have revealed the two major classes of anti-tumour therapeutics: i) Application of molecularly targeted therapeutics to block hallmarks of cancer, and ii) Employing drug delivery systems through tumour-targeted nanomedicine to improve the pharmacokinetics and bioavailability of vehicle-carried drugs. The US Food and Drug Administration (FDA) approved the first anti-CD20 mAb (Rituximab) for the treatment of non-Hodgkin's lymphoma in 1997. To date, 12 of these anticancer molecular-targeted mAb's have been approved worldwide. Nanotechnology for cancer is expected to transform current treatment systems by providing more efficient cancer diagnostics and therapeutics.[35-39]

Now a days, nanocarriers are utilized in investigating cancer associate at early stage, delivering tumor medicine specifically to malignant cells, and find out these drugs are killing malignant cells or not. Two therapeutic nanocarrier-liposomes and simple protein

nanoparticles are approved by North American country (USFDA) government agency for clinical practices. As nanocarriers are evaluated for safety and efficaciousness, this can bring with it important advances in molecular imaging and specific targeting of neoplasm therapeutic agents, elevating therapeutic efficaciousness, and finally achieving the goal of early detection and management of cancer. Customized nanoscale constructs will function targeted drug delivery vehicles capable of delivering massive doses of radionuclide or chemotherapeutical agents into malignant cells whereas economical traditional tissues, greatly reducing the side-effects that typically accompany several current cancer therapies.

Monoclonal antibody-guided radiation therapy, or radio immunotherapy, demonstrated two radiolabel anti-CD20 monoclonal antibodies ^{90}Y-ibritumomab (Zevalin®) and ^{131}I-tositumomab (Bexxar®) were approved by the US FDA in 2002 and 2003, respectively, for treatment of B-cell non-Hodgkin's lymphoma (NHL), which indicates the potential benefit of antibody-guided systemic radionuclide-targeted therapy. Emerging new methods improve the specific uptake of radio nuclides in tumour cells while sparing the normal tissues. Several advanced strategies for radio nuclides delivery have been studied extensively, including the combination of chemotherapy agents with particle-emitting radio nuclides and the development of novel multimodality and multifunctional therapeutics. Optimization of treatment protocols has significantly improved the therapeutic efficacy and reduced the toxicity to normal tissues. Nanoparticles delivering radionuclide for improving pharmacokinetics and therapeutic efficacy of cancer.[3-13]

The selection of potential radio nuclides for tumour imaging and radionuclide radiotherapy involves the physical half-life, decay mode and the emission properties of the radionuclide **shown in figure 3.**

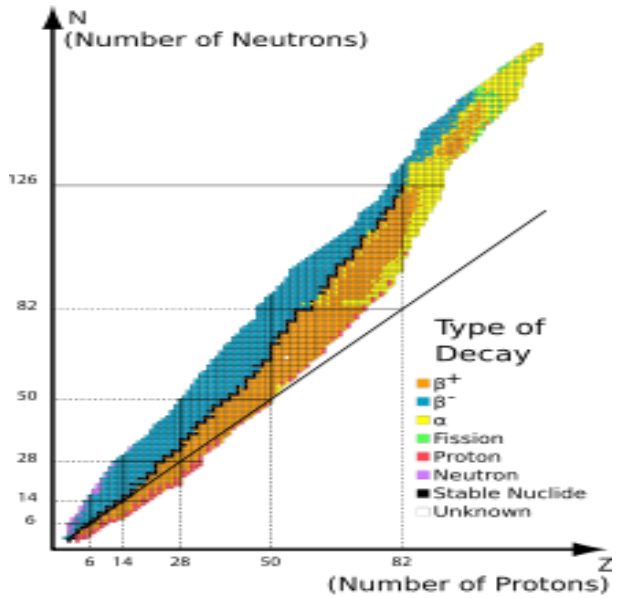


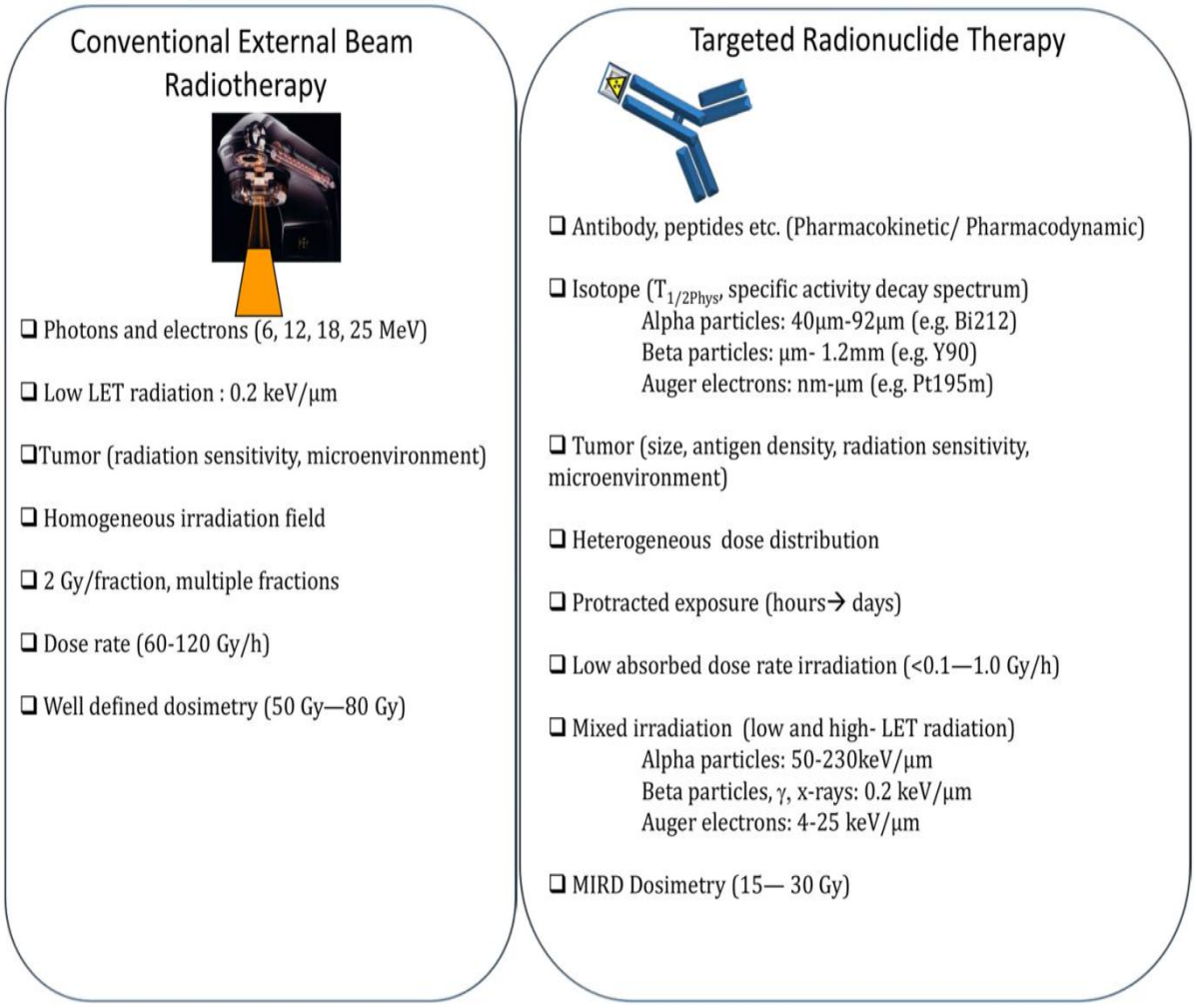
FIG. 3: Decay mode of the protons.

Gamma emitters with energy in the 150 keV range can be used for gamma imaging or single photon-emission tomography (SPECT), and high energy positron-emitters with energy at 511 keV energy can be applied for positron-emission tomography (PET). For targeted radionuclide radiotherapy applications, high and low energy β-emitters are ideal radioisotopes for the treatment of small to large clusters of tumour cells. The tissue penetration ranges (1-10 mm) and cross fire effect of β-particles can kill tumour cells in close proximity to neovasculature. Alpha-emitters hold great promise as therapeutics for small cancer lesions and micro metastatic cancers due to the high linear energy transfer (LET, 80keV/µm) and short range energy depositions with tissue penetration range of 50-100 µm. Monoclonal antibody labelled with α-emitters has been demonstrated to have high specific killing effects and minimal normal-tissue damage in a tumour-bearing animal model. Auger electrons have an energy of <30 keV and sub cellular path length of 2-12 µm. Thus, auger electron emitters can exert their radiotoxic effects on cells only when they are internalized into the cytoplasm.[16]

Targeted radionuclide therapy is often limited by insufficient delivery of radionuclide to tumour sites using the currently available targeting strategies, such as monoclonal antibodies and peptides, due to relatively low and heterogeneous expression of receptor on tumour cells, as well as dose-limiting toxicities to normal tissues. To maximize the therapeutic index and to minimize the outcome of toxicity, it is very important to deliver the radionuclide to the right site at the right concentration and at the right time. The rapidly advancing field of cancer nanotechnology has generated several innovative drug delivery systems, such as liposome, dendrimers, quantum dots, iron oxide and carbon nanotubes, to improve and enhance targeted transport of cytotoxic drugs and radio nuclides to tumour lesions. These nanocarriers systems could provide the delivery platforms needed for improving the delivery of radionuclide to tumour sites. Nanocarriers' delivery systems have also revealed enhanced imaging and therapeutic efficacy by targeted delivery of drugs to the tumour site and by reducing their toxic side-effects. Major advantages of nanocarriers are that they can be prepared in sizes <100 nm, and selectively increase the localization of drugs and radionuclide in the tumour through passive targeting or active targeting, while sparing non-targeted tissue, ensuring minimal drug or radionuclide leakage during circulation, and facilitating intracellular drug or radionuclide delivery and uptake for active targeting. There are three generations of nanocarriers: i) The first generation of nanocarriers (passive targeting) which are rapidly trapped in the recticuloendothelial system (RES) organs (*e.g.* liver and/or spleen); ii) The second generation of pegylated nanocarriers (passive targeting), which can evade the RES of the liver and spleen, enjoys a prolonged circulation in the blood and allows for passive targeting through the enhanced permeability and retention (EPR)

effect in leaky tumour tissues; iii) The third generation of nanocarriers (active targeting) has a bio conjugated surface modification using specific antibodies or peptides to actively targeted specific tumour or tissues. The pharmacokinetics and bioavailability of drugs and radionuclide delivered by the third generation of nanocarriers were much improved. One of the major challenges is to design a nanocarriers with less immunotoxic effect and to avoid higher biological barriers in the body such as to reduce delivered diagnostic and therapeutic agent uptake in the recticuloendothelial system (RES). There are five approaches generally used for labelling or encapsulating radionuclide on nanocarriers: i) Labelling nanocarriers by encapsulation during preparation; ii) nanocarriers surface labelling after preparation; iii) nanocarriers surface labelling of bio conjugates after preparation; iv) incorporation into the lipid bilayer after preparation; and v) after-loading of the aqueous phase of the nanocarriers after preparation. The after-loading method has provided higher labelling efficiencies (>90%) and the greatest *in vivo* stability for ^{99m}Tc, ^{111}In, and ^{67}Ga radionuclide for nuclear imaging. Liposomes are spherical bilayer of small phospholipids vesicles which spontaneously form when water is added to a dried lipid mixture. Significant progress has been made in the use of liposome as nanocarriers for the delivery of imaging radionuclide. The ability to modify the surface of nanocarriers permits improvement in the pharmacokinetics, bioavailability, toxicity and customization of nanocarriers' formulations for particular tumour imaging agents.[28]

Delivery of ^{99m}Tc, ^{111}In and ^{67}Ga radionuclide by liposome for gamma-imaging and monitoring drug treatment have been reviewed and reported. The biodistribution, pharmacokinetics and nuclear imaging of ^{111}In-DTPA-labeled pegylated liposome were studied in patients with advanced local cancer.



Effective targeting of solid tumours of breast, head and neck, lung, brain and cervix were also observed with gamma camera and SPECT imaging. Liposome encapsulating the positron-emitter ^{18}F-FDG was applicable for diagnostic imaging and real-time liposomal tracking *in vivo*. Enhanced tumour accumulation and visualization by γ-scintigraphy with ^{111}In-labeled nucleosome-specific monoclonal antibody 2C5 bio conjugated immunoliposome has been studied, and the results indicated better and faster imaging in various tumour-bearing mice in shown figure 4.

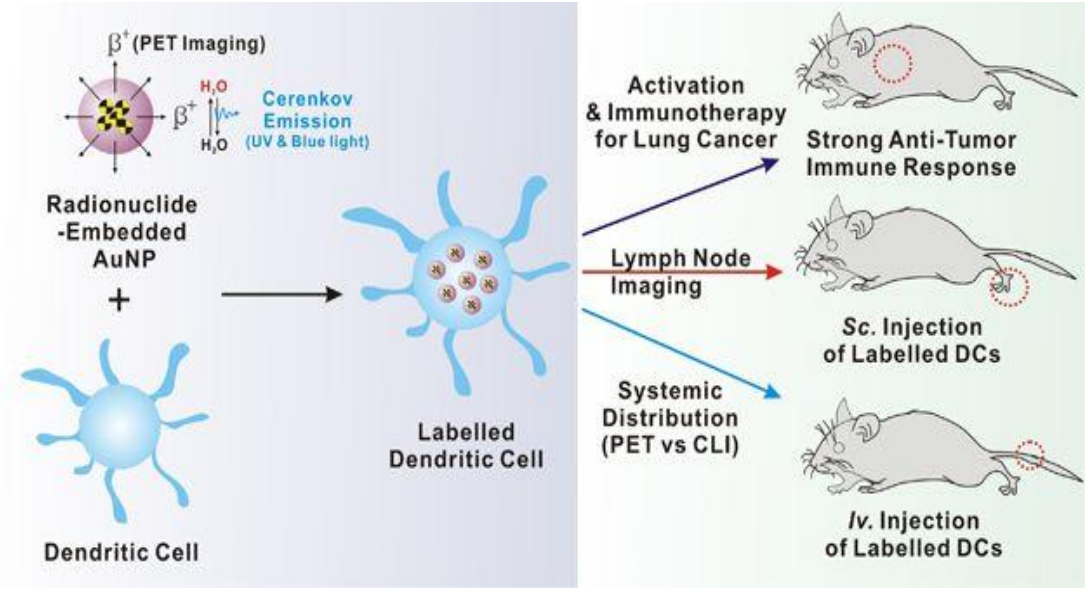


FIG. 4: In-Labelled MAbs Through Different Routes.

Typically, nanotargeted radiopharmaceuticals have a two-component architecture for passive targeting therapeutics, *e.g.* a pegylated nanoliposome loaded with radionuclide payloads, and three-component architecture for active targeting therapeutics, such as pegylated nanoliposome bio conjugated with targeting antibody or peptide and encapsulated radionuclide payloads. An analysis suggested that chemotherapy delivery is differ from optimal liposome system for radiotherapy. In this study for the use of radionuclide ^{131}I, ^{90}Y, ^{188}Re, and ^{67}Cu labelled liposome for internal radiotherapy has been reported. The results of the effective targeting of solid tumours in patients with advanced local cancer by radiolabel pegylated liposome support the possibility of the delivery of β-emitting radionuclide loaded pegylated liposome for the treatment of solid tumours.[23]

A standard approach to the first phase of ovarian cancer treatment is abdominal surgery followed by carboplatin-paclitaxel chemotherapy. A novel approach for next-generation clinical trials seeks to incorporate targeted radiopharmaceuticals that integrated into first-line treatment either to augment chemotherapy effects or to eradicate chemotherapy insensitive but radiation sensitive disease. There is historical precedence for such an approach e.g. In four randomized clinical trials of women with advanced stage ovarian cancer; intrabdominal instillation of the β-particle emitter ^{32}P chromic phosphate was studied. ^{32}P chromic phosphate as a single infusion was well-tolerated and deemed clinically beneficial. The further clinical development of early radiopharmaceuticals was stopped due to clunky logistics for ^{32}P chromic phosphate instillation and a clinical desire to test newer chemotherapy agents. Targeted α-particle radiopharmaceutical conjugates combine the affinity and specificity of molecular targeting with cytotoxic energy-rich radiation delivered anywhere in the body to cancer cells and their microenvironment for disease control .As expected, the radioactive payload of targeted α-particle radiopharmaceutical conjugates drives the efficacy and toxicity of these agents. But, there is also the possibility that the targeting ligand and cleaved/non-cleaved chemical linkers may also contribute to organ-specific toxicity. These radioactive drugs aim for accurate and precise molecular delivery of energy-rich radiation to cancer cells either circulating in the blood or in tumours. Radiopharmaceuticals are either neat (i.e., lack a targeting ligand) or conjugated (i.e., have a ligand-linker-payload construct). The radiopharmaceutical radium-223 dichloride falls into the neat class. This is because it is given by vein as a slow bolus solution that tracks to areas of bone turnover as calcium mimetic without the aid of a ligand. In an opposite way, thorium-227-containing radiopharmaceuticals (the parent radionuclide of radium-223) are in the conjugated class. This conjugated molecular entity has three components—a radioactive payload, a linker, and an antibody. Each component possibly contributes to its safety profile. For this reason, NCI has adopted the approach for conjugated radiopharmaceuticals to consider the safety of radionuclide, its cleaved/non-cleaved linker, and "cold" radiopharmaceutical antibody prior to launching clinical trials of the radiopharmaceutical. Thorium-227 has begun clinical trial testing among women with advanced stage ovarian cancer. Thorium-227 can be encased by octadentate chelates of the 3,2 hydroxypyridinone (3,2-HOPO) class. As an alpha-particle emitting radionuclide, it is a highly potent cytotoxic payload. Given that general knowledge of organ-specific radiation-induced toxicities are sufficient to address safety from radionuclide radioactivity; the path for the thorium-227 anti-mesothelin monoclonal antibody conjugate radiopharmaceutical to enter the clinic was relatively straightforward. In a clinical study, a radiopharmaceutical like this might possibly associate with exhaustion, low blood cell or platelet count, gastrointestinal upset, or even specific normal organ

toxicity due to the normal expression of the targeted antigen. The thorium-227 anti-mesothelin monoclonal antibody conjugate radiopharmaceutical uses a 3,2-HOPO chelates to house thorium-227 and link it to a tumour-targeting antibody, and in this case, against mesothelin. As anetumab ravtansin this antibody has undergone prior clinical development. Usual radiochemical purity is 99 percent or greater, meaning the 3,2-HOPO chelates linker-antibody is in excess of the thorium-227. Linker chemistry is important to the distribution of a radioactive payload. While linker as a molecular entity may not contribute to the frequency, severity, or interference of radiopharmaceutical-related toxicity, the stability of the linker does have an impact upon which organs or tissue are affected. Stable non-cleaved linkers restrict payloads to targets for narrow toxicity profiles, whilst less stable cleaved linkers might allow payloads to drift away from targets creating much broader toxicity. Cleavable linkers typically release payloads after processing in endosomes or lysosomes via a variety of mechanisms including acidic degradation, protease cleavage, and thiol-disulfide exchange reactions. The thorium-227 anti-mesothelin monoclonal antibody conjugate radiopharmaceutical is viewed as not having a cleavable linker. And so, complete lysosomal degradation of the antibody, alpha-particle mediated damage to the 3,2-HOPO chelates, or loss of decayed daughter radionuclide must manifest for unintended organ or tissue toxicity. Radiopharmaceutical antibody chemistry demands high affinity target antigen binding for tumour cells and low affinity for normal cells for a realistic therapeutic window. It is therefore desirable for cancer cell-directed antibodies to seek antigens expressed on the surface of those cancer cells prior to internalization and endosomal processing. But, target antigen might also expressed by normal cells.[23-29]

An illustrative example is antigen mesothelin which found on the surface of some normal cells like the abdominal peritoneum, lung pleura, eye cornea/limbus, and heart pericardium is also found in ovarian cancers. In "Cold" pharmaceutical ligand may reflect non-specific or inappropriate target antigen recognition on normal cells, but might have off-target biological effects. Off-target effects might manifest as toxicity. In the example of thorium-227 anti-mesothelin monoclonal antibody conjugate, the "cold" 3, 2-HOPO chelates-antibody pharmaceutical toxicity has not been well-characterized. It bears to reiterate that low level target antigen expression on normal cells may result in specific toxicity, and, cleavage or damage to the linker may induce unintended organ toxicities from free radionuclide. One Category C CTCAE example is fatigue. Radiation exposure has been shown to unregulated expression of nucleoside transporters and kinases in cancer cells, perhaps rescuing cells from replication stress. It has been speculated that radiation-related exhaustion might result from skeletal muscle expending energy to furnish deoxynucleosides via the bloodstream to irradiated cells demanding their supply for DNA repair. There may be an opportunity to study circulating deoxynucleosides levels further as biomarkers of response in women with chemo refractory advanced stage ovarian cancer treated by radiopharmaceuticals. Anaemia, leucopoenia or neutropenia, and thrombocytopenia from enhanced elimination or impaired production of marrow constituents, and not circulating mature cells or platelets, are Category A CTCAE acute or cumulative toxicity effects. Pneumonitis or eye corneal/limbic keratitis represent two transient, reversible, or persistent Category B CTCAE sub acute toxicity effects attributable in a 3-month window following radiopharmaceutical exposure.[41-47]

APPLICATION IN MEDICINES

Radioactive Isotopes	Applications in Medicine
Cobalt-60	Radiation therapy to prevent cancer
Iodine-131	Locate brain tumours, monitor cardiac, liver and thyroid activity
Carbon-14	Study metabolism changes for patients with diabetes, gout and anaemia
Carbon-11	Tagged onto glucose to monitor organs during a PET scan
Sodium-24	Study blood circulation
Thallium-201	Determine damage in heart tissue, detection of tumours
Technetium-99m	Locate brain tumours and damaged heart cells, radiotracer in medical diagnostics (imaging of organs and blood flow studies)

CONCLUSION

In summary, this article provides Radiopharmaceuticals can also be used to diagnose certain cancers, as oncologists can track radioactivity throughout the body after the drugs are administered to determine if cancer is present. Gamma camera or a similar gamma imaging device are special imaging system that are used for diagnostic purpose. The term "Tracers" is used for radiopharmaceuticals used in diagnostic purposes. Usually the tracers contain smaller amounts of radiation. Teletherapy and brachytherapy is the old 19th century technique to treat the cancer with increased level of risk of toxicity or reduce effect of therapy which will not ensure the treatment due to dose. But the current techniques not only providing ensure treatment but also with the less adverse event or side effect. Like Concomitant chemotherapy and radiotherapy has been illustrated to improve treatment outcome in a range of solid tumours. Pegylated liposome-encapsulation of doxorubicin and cisplatin has been shown to target drugs to tumours, increase therapeutic efficacy and reduce toxicity. Trimodal cancer therapy combining anti-angiogenesis, chemotherapy and radiotherapy has beneficial effects and is emerging as a clinical antitumor

strategy. Image-guided and passive nanocarriers-based polymeric nanomedicine for radiotherapy holds significant potential for improving the treatment of advanced solid tumours. Biodistribution, pharmacokinetics, and nuclear imaging of passive nanotargeted radio-therapeutics.

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