Role of nuclear medicine in cancer therapy

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Abstract

Nuclear medicine is a multidisciplinary field that develops and uses instrumentation and tracers (radio pharmaceuticals) to study physiological processes and non-invasively diagnose, stage, and treat diseases. Particularly, it offers a unique means to study cancer biology in-vivo and to optimize cancer therapy for individual patients. A tracer is either a radio nuclide alone, such as iodine-131 or a radiolabel in a carrier molecule such as F-18 in fluoro deoxyglucose, or other feasible radio nuclide attached to a drug, a protein, or a peptide, which when introduced into the body, would accumulate in the tissue of interest. Nuclear medicine imaging, including single-photon emission computer tomography and positron emission tomography, can provide important quantitative and functional information about normal tissues or disease conditions, in contrast to conventional, anatomical imaging techniques such as ultra-sound, computed tomography, or magnetic resonance imaging. For treatment, tumor-targeting agents, conjugated with therapeutic radio nuclides, may be used to deposit lethal radiation at tumor sites. This review outlines the role of nuclear medicine in therapeutic treatment of cancer.

1 Introduction

Nuclear medicine therapy is a cancer treatment that uses radioactive drugs that bind to cancer cells and destroy them. This therapy is an option for some people with neuroendocrine tumors, prostate cancer, meningiomas, thyroid cancer and lymphoma. It has proved to be successful in easing symptoms, improving quality of life and extending life. Nuclear medicine therapy is an approach to treating cancer that might be used with or after other treatment

options, such as chemotherapy and surgery. It won't usually lead to a cure unless combined with other therapies. But for many people it will control symptoms and shrink and stabilize the tumors, sometimes for years. Nuclear medicine therapy is sometimes the best option for people who no longer respond to other treatments.

What makes nuclear medicine therapy effective is the use of radioactive molecules as a drug (molecular radiotherapy). The drug recognizes tumor cells. It's injected intravenously, then circulates in the body, sticks to the tumor cells, delivers radiation directly and causes them to die. Some of the drug never attaches to cancer cells and keeps floating in the blood until the body gets rid of it, mostly in the urine. Over time, the radioactive drug stops giving off radioactivity and stops killing cancer cells. Nuclear medicine therapy is often repeated multiple times to achieve the most benefit.

Nuclear medicine therapy is also called peptide receptor radio-nuclide therapy (PRRT), targeted radiotherapy, radio-nuclide therapy, therapeutic nuclear medicine and a theranostic approach to treating cancer.

Nuclear medicine therapy uses radiopharmaceuticals targeting specific tumours, such as thyroid, lymphomas or bone metastases, delivering radiation to tumorous lesions as part of a therapeutic strategy to cure, mitigate or control the disease. It can be used either on selective targets or throughout the entire body.

Targeting the tumour :- The advancements in medical technology have led to a dramatic surge in the development and availability of new cancer treatments. The treatment of cancer involves different strategies, such as chemotherapy, surgery, radiation therapy and, most recently, targeted therapies, such as the use of radionuclide-based therapies employed in nuclear medicine. External radiotherapy with ionizing radiation is the most frequently employed radiation treatment of cancer patients. In this approach, the primary tumour and a limited area around it is treated through irradiation with high-energy X-rays.

Another treatment option available for certain types of cancer is the use of targeted radionuclide therapy, which is based on administering radioactive substances to patients. Just like chemotherapy, this therapy is a systemic treatment, reaching cells throughout the body by travelling through the bloodstream. However, unlike chemotherapy, these radioactive substances specifically target diseased cells, thus reducing potential side effects.

Radiopharmaceuticals :- The radiopharmaceuticals suited for therapeutic purposes are those that strongly bind with the tumour – also known as vehicles with a high tumour affinity. They can transport targeted doses of radiation directly to the tumours and its metastases, thereby sparing normal healthy tissue. The choice of the molecule that carries the radiation to the

tumour is determined by its affinity – or binding power – to the tumour's target structures, such as antigens or receptors. The ionizing radiation emitted by radionuclides linked to the carrier kill cancer cells by damaging their DNA, causing the tumours to shrink.

An ideal radiopharmaceutical for therapeutic purposes should:

- act exclusively in the cells of malignant tumours;
- reach all the cells of malignant tumours wherever they are localized;
- leave healthy tissues and organs unhurt while bringing maximum doses of radiation to the tumour;
- eliminate malignant tumour cells with great effectiveness.

How the therapy works :- The biological action of a radiopharmaceutical is determined by the form of ionizing radiation emitted by the radionuclide. While imaging procedures in nuclear medicine require radionuclides that will emit (gamma) radiation able to penetrate the body, a different class of radionuclides possessing optimal relative biological effectiveness is needed for radionuclide therapy. The radionuclides best suited for tumour therapy are those emitting ionizing radiation with short penetration into the tissue, such as (alpha) or (beta) emitters, which release their energy in the proximity of their targets.

2 Progression

2.1 Nuclear Medicine for Cancer Diagnosis and Treatment

Nuclear medicine can help diagnose and treat different conditions, including some forms of cancer.

In nuclear medicine, doctors put small amounts of radioactive material into your body so they can see your organs and tissues, as well as how well they work. That can help them spot tumors and see if your cancer has spread to other areas of your body. It can also help target cancer cells.

Doctors also use nuclear medicine to see if a treatment is working.

2.2 How It Diagnoses Cancer

Like X-rays, nuclear medicine is a type of radiology. But while X-rays give doctors a "big picture" view of your anatomy, nuclear imaging shows the amount of activity in your organs and tissues.

When doctors use nuclear medicine to diagnose or monitor a disease like cancer, they put things in your body called radionuclides (or "tracers") that release low levels of radiation.

You can take radionuclides by mouth or through an intravenous (IV) drip. After you take these radionuclides, you'll have what's called a nuclear scan. Scans take pictures of a specific area of your body to help doctors find tumors and other things, like infection. For example, a tumor may show up as a "hot spot" on the picture, meaning the radiation collects in greater amounts in areas where the tumor is active. Or a tumor might show up as a "cold spot," meaning there's actually less cell activity. That can also be a sign of cancer.

The type of scan you receive depends on what your doctors want to see. Some of the more common types of scans used to diagnose and monitor cancer include:

Bone scans : These look for cancer that has gone to your bones from other areas of your body. Nuclear medicine can sometimes find signs of bone cancer earlier than X-rays can. **Gallium scans:** A radioactive substance called gallium goes into your vein through an IV.It can help your doctor spot cancer throughout your body. Gallium scans can also find other problems, like infection or inflammation.

MUGA scans: Doctors use radionuclides to see how your heart is pumping blood. That helps them figure out how well your heart works before, during, and after certain types of chemotherapy. That's important because chemotherapy, particularly high amounts of it, can affect how well your heart works.

PET (positron emission tomography)scan : When you have this, you get an IV injection of radioactive sugar. The amount of that sugar that your cells absorb can help your doctors learn how fast your cancer cells are growing. In some cases, you would get PET scans along with computerized tomography (CT) scans. Together, these tests help doctors figure out exactly where your tumors are.

Thyroid scans : To get one of these, you swallow radioactive iodine or receive an injection. The iodine collects in your thyroid gland and helps doctors find thyroid cancer.

Nuclear medicine scans aren't painful. The scans usually involve lying on a table while a doughnut-shaped scanning machine takes photos. The whole thing usually takes 30 minutes to an hour. In some cases, you may need to

stop eating or drinking for a certain amount of time before your scan.

2.3 How Nuclear Medicine Treats Cancer

There are several types of nuclear medicine that treat cancer. They include:

Radioimmunotherapy : If you have non-Hodgkin's lymphoma that doesn't respond to chemotherapy, your doctor may recommend this, also called RIT.

It combines radiation therapy and something called immunotherapy, a type of treatment that uses your body's immune system to fight your cancer. Through an IV, a doctor gives you something called monoclonal antibodies. These are man-made proteins that target certain parts of cancer cells. You also get a radioactive substance attached to those antibodies.

Together, these things latch on to cancer cells and deliver radiation directly to the tumor to kill it.

Researchers are looking to see if radioimmunotherapy can help with other cancers, like:

- Prostate cancer
- Melanoma
- Leukemia
- Colorectal cancer
- High-grade brain glioma

Radioactive iodine therapy : Your thyroid gland absorbs almost all the iodine you take in. In this treatment, radioactive iodine (also known as RAI or I-131) collects in thyroid cells, where it destroys the gland and the cells.

Unlike some other forms of radiation, radioactive iodine (also known as radioiodine) therapy does this without hurting the rest of your body. Doctors often use radioactive iodine to destroy thyroid tissue that surgery can't remove. It sometimes also helps kill thyroid cancer cells that have spread to your lymph nodes or other parts of the body.

Brachytherapy : This procedure involves delivering high doses of radioactive material inside your body to kill cancer cells. In most cases, brachytherapy is more targeted, causes fewer side effects, and has doesn't take as long as conventional radiation therapy, which uses an external beam outside of your body to project radiation into your cells.

Sometimes, you'll get brachytherapy with other forms of cancer treatment, like chemotherapy or surgery.

Brachytherapy treats several types of cancer, including:

1. Bile duct cancer
2. Brain cancer
3. Breast cancer
4. Cervical cancer
5. Endometrial cancer
6. Esophageal cancer
7. Eye cancer
8. Head and neck cancers
9. Lung cancer
10. Pancreatic cancer
11. Prostate cancer
12. Rectal cancer
13. Skin cancer
14. Soft tissue cancers
15. Vaginal cancer

Y90 radioembolization: This liver cancer treatment happens in two steps. In the first, a catheter goes in the artery that supplies blood to your liver. Your doctor then uses a special dye so they can "map out" the other arteries that have anything to do with your liver. The second step is when the radiation goes in. It's put onto tiny particles that can be made of glass or resin. Then, after double-checking the positioning, the radiation goes into the liver artery. The particles stick into the cancer and release the radiation directly into the tumor.

3 Imaging methods

There are three different functional imaging techniques under the general umbrella of nuclear medicine. The most Table 1 Examples of significant discoveries in nuclear medicine 1930s E.O. Lawrence developed the cyclotron at the UC Radiation Laboratory that later on produced the first medically useful radionuclides, including iodine-131, thallium-201, technetium-99 m, carbon-14, and gallium-67 1940s The first reactor-produced radionuclides for medical research were made at Oak Ridge National Laboratory (ORNL) including phosphorous-32, iron-52, and chromium-51 1950s Benedict Cassen invented the first automated scanner at the University of California at Los Angeles (UCLA) to image the thyroid gland after administering radioiodine to patients Hal Anger invented the stationary gamma camera (now known as the Anger camera) at the UC Radiation Laboratory The molybdenum-99/technetium-99 m generator was developed at Brookhaven National Laboratory (BNL) by Powell Richards 1960s Scientists at ORNL discovered the affinity of gallium-67 for soft-tissue tumors. This radionuclide had been used to image lymphomas, lung cancer, and brain tumors 1970s PET scanners were developed by Michael Phelps, Edward Hoffman, and Michel Ter-Pogossian at Washington University based on earlier work by Gordon Brownell at the Massachusetts Institute of Technology (MIT) and James Robertson at BNL 18F-FDG, a positron-emitting compound, was synthesized by chemists at BNL Scientists at the University of Pennsylvania and at the NIH used 18F-FDG to image glucose metabolism in the human brain 1980s A new radiopharmaceutical, iodine-131-m-iodine-benzyl-guanidine (I-131 MIBG), was developed by Donald Wieland for the diagnosis and treatment of rare childhood cancers Michael Welch of Washington University and John Katzenellenbogen of the University of Illinois developed the first PET radiotracer used to image tumors expressing the estrogen receptor 1990s A high-resolution PET scanner designed to image small laboratory animals (i.e., microPET) was developed at UCLA by Simon Cherry Radiolabeled antibodies were developed for therapy Advances were made in the application of alpha-particle emitters for therapy Tumor Biol. Author's personal copy basic is planar scintigraphy that provides information about the distribution of radioactive material in a single twodimensional image, analogues to a planar X-ray scan. As computer tomography presents three-dimensional anatomical images, single photon emission computed tomography (SPECT) uses a series of contiguous two-dimensional images of the distribution of the radiotracer using the same agents as planar scintigraphy to provide a three-dimensional distribution of radiotracers. Finally, the most sensitive method, PET, utilizes -rays produced in the process of positron–electron annihilation

and requires radionuclides emitting positrons. PET and SPECT have very high sensitivity as they allow detection of radiolabeled probe molecules in the 1011– 1012 and 1010–1011 range, respectively. This high sensitivity allows obtaining high-quality three-dimensional images, particularly useful for the detection and characterization of neoplasm. The noninvasive molecular imaging techniques complement well-established ex vivo assays, such as immunohistochemistry, fluorescence in situ hybridization, or enzymelinked immunosorbent assay, which require invasive sampling procedures and, because of tissue heterogeneity, may not always adequately represent the biochemical or pathological processes

4 Radionuclides

The choice of a radionuclide depends on particular application. While radionuclides used for nuclear medicine imaging emit -rays, which can penetrate deeply into the body, the radionuclides used for therapy must emit radiation with relatively short path length in order to deposit their energy locally and minimize the whole-body irradiation. There are three types of particulate radiation of consequence for radionuclide therapy—beta particles, alpha particles, and Auger electrons. The physical half-life of the radionuclide should match the biological half-life of the labeled monoclonal antibody (mAb), mAb fragments, small peptides, or small organic molecules to achieve the optimal SNR. In practice, the half-life of the selected isotope should be, at a minimum, twofold longer than the biological half-life of the event kinetics to be imaged . Its production should be rather easy and cheap. In addition, chemical properties of radionuclide should facilitate labeling and prevent accumulation of radioactivity in nontargeted organs. Following are the main categories of radionuclide utilized in nuclear medicine.

Photon emitters The radionuclides used in SPECT imaging emit -rays with energies in the range of 30 to 300 keV and have longer half-lives (from hours to several days) as compared to the typical rapidly decaying positron-emitting isotopes used in PET. They are commercially available, which makes them relatively cheap and easy to handle. The radiometal technetium-99 m (99mTc) is so far the most commonly used radionuclide in nuclear medicine due to its favorable physical properties (T1/206 h, E0140 keV) for diagnostic imaging and its widespread availability as a column elute from commercially 99Mo/99mTc generators. Apart from 99mTc, the other commonly used -emitting radionuclides are gallium-67 (67Ga), indium-111 (111In), and iodine-123 (123I). Since -radionuclides have their own spectra, SPECT imag-

ing has the unique capability of imaging multiple probes labeled with different isotopes allowing the simultaneous study of multiple cellular or molecular events. Positron emitters The most common cyclotron-produced, positron-emitting radionuclides are common elements found in biologically active molecules and pharmaceuticals. Carbon11 (11C, T1/2020.4 min), nitrogen-13 (13N, T1/209.96 min), oxygen-15 (15O, T1/202.05 min), and fluorine-18 (18F, T1/20 109.7 min). They all have short a half-life, which often complicates the radiolabeling process but also has a few advantages. The absorbed radiation dose to the patient being studied is generally less than with a longer-lived tracer, allowing more amount of the tracer to be injected that in turn increases the SNR. Furthermore, more than one study may be performed on the same patient, even on the same day since the tracer radioactivity decays quickly. On the other hand, their short half-lives limit their use to institutions that have cyclotron, a radiochemical laboratory, and PET scanner located near each other so that imaging studies can be completed before the radioactivity decays.

There is also a lot of interest in gallium-68 (68Ga, T1/20 68 min), a metallic positron emitter, produced from a generator with a rather long-lived mother nuclide, 68Ge (T1/20 270.8 days). It provides a convenient alternative, especially to 18F-labeled compounds, in the places where access to a cyclotron is limited. The short half-life of radionuclides allows mainly for labeling of small molecules and peptides with very rapid kinetics. Other, less commonly used cyclotron-produced isotopes, having much longer half-life include copper-64 (64Cu, T1/20 12.7 h), yttrium-86 (86Y, T1/2014.7 h), bromine-76 (76Br, T1/20 16.1 h), zirconium-89 (89Zr, T1/2078.4 h), and iodine-124 (124I, T1/204.18 days). They are particularly suitable in combination with intact mAbs because they match well to their biological half-lives, giving optimal contrast for imaging purposes. The characteristics of the most commonly used positronemitting radionuclides. Beta emitters Beta emitters are commonly used radiotherapeutics, since they have relatively long path length (0.8–5 mm) and low linear energy transfer (LET) of approximately 0.2 keV/m. The long range results in a pronounced cross-firing effect which may affect antigennegative, tumor cells but also contributes to nonspecific toxicity of nontargeted tissues. These properties make beta emitters such as 90Y or 188Re more suitable for treating poorly perfused, bulky tumors but less suited for targeting small metastases as their energy would be deposited outside of the target volume. In this case, low-energy -rays as those emitted by 177Lu would be more efficient. Of course, for conjugation purposes, the half-life of these particles need to match the pharmacokinetic properties of particular targeting agents, even though there are some indications that longer half-life of therapeutic radionuclides might be advantageous.

The broad scope of preclinical and clinical research in the therapy field also involves holmium-166, rhenium-186, copper-67, promethium-149, gold-199, and rhodium-105. Also, low-energy Auger electrons, resulting from electron capture or isomeric transition decay, are investigated. Most commonly used Auger electron emitters are bromine77, indium-111, iodine-123, and iodine-125. When used in concert with targeting vehicles that can localize these subcellular-range radiations in close proximity to cellular DNA, studies in cell culture have shown highly effective and specific tumor cell killing. Alpha emitters Alpha particles have much higher energy (4–9 MeV) but travel in tissue over only a few cell diameters (i.e., 40–100 m), offering the exciting prospect of matching the cell-specific nature of molecular targeting with radiation of a similar range of action. Another attractive feature of alpha particles for targeted radionuclide therapy is that, due to their size and charge, the energy is deposited at relatively short distances resulting in high LET (100 keV/ m). In fact, alpha particles loose 100 to 1,000 times more energy, via relatively dense ionization events, while traversing DNA than either conventional external beam X-ray radiation or beta particles do. Since the average distance between ionization events matches the distance between the two strands of DNA, the high LET of alpha particles is effective in creating double-strand breaks in DNA, and therefore, quiescent cells are also affected by this process. Over the last decade, application of alpha emitters for targeted radionuclide therapy has been actively investigated. Studies have been done with bismuth-213- and astatine-211- labeled monoclonal antibodies in patients with leukemia and brain tumors, respectively, and radium-223 chloride was evaluated in breast and prostate cancer patients with bone metastases. Recently, there is a growing interest in using actinium-255, a radionuclide that generates four net alpha particle isotopes in a short decay chain to stable bismuth-209, as a source of therapeutic alpha particles. Actinium-255-labeled antibodies are being tested in patients with advanced myeloid malignances. The results of clinical trials using alpha emitter-containing radiopharmaceuticals indicate that this therapeutic strategy presents a promising alternative for the treatment of cancer.

5 Radiotracers

Small molecules Fluorine-18-2-fluoro-2-deoxy-D-glucose (18F-FDG) is a radiolabeled glucose analogue. This nontumor-specific molecule that visualizes the glucose metabolism, often increased in tumor cells as compared to normal cells, is by far the most widely used (¿90 glucose metabolism is not specific for malignant processes, physiologic 18F-FDG uptake occurs in

normal tissues (brain, muscles, salivary gland, myocardium, urinary tract). It is also taken up by different inflammatory as well as benign lesions, which potentially could lead to falsepositive or false-negative findings. A large number of studies clearly demonstrate that 18F-FDG imaging had improved staging and detection of recurrence in oncology, and several excellent papers reviewing such data have already been published. 18F-labeled thymidine analogue 3-deoxy-3-[18F]-fluorothymidine (18F-FLT) is transported across cell membranes by nucleoside transporter proteins and retained in the cell after phosphorylation by thymidine kinase 1 (TK1), whose levels correlate with cell proliferation. Similarly, to 18F-FDG, the phosphorylated 18F-FLT is trapped intracellularly but is not further incorporated into the DNA. It has been demonstrated in many types of cancer that 18F-FLT uptake in vivo is a measure of tumor proliferation. Beyond this, 18F-FLT uptake is dependent on TK1 activity through the activation of a salvage pathway that does not correlate with cell proliferation in all tumor types. This lack of correlation could explain the variances in response between different cancer types, since in some the de novo pathway seems to be dominant