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A REVIEW ON THE ROLE OF RADIOPHARMACEUTICALS IN THE TREATMENT OF CANCER: THE RADIATION THERAPY

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ABSTRACT
Radioactive agents are employed in nuclear field for demonstration of high and exact localized radioactive effect in a particular target tissue. In recent times various amount of radionuclide and radiopharmaceuticals are employed for treating cancer and other complex disease like neuroendocrine disorder. Its application is not just confined to treatment of diseases but it is also establishing roots in field of diagnosis. This review focuses on understanding the development of radiopharmaceuticals and their application in treatment of cancer.

KEYWORDS: Radiopharmaceuticals, Radionuclide, Ionizing and Non- Ionizing Radiation, Cancer, Cell- Cycle, Radio- labelled, Monoclonal Antibodies.

INTRODUCTION

Radiopharmaceuticals

Radiopharmaceuticals are biologically active molecules labeled by radionuclides which provide a beneficial source of ionizing radiation mainly applied in diagnostic imaging and therapy. Short-lived radionuclides emitting either β^+ particles (positrons) or γ-rays are employed in diagnosis, whereas Auger electrons and α/ β^- (electrons) emitters are administered in therapy.

The Radiation Therapy

Working of Radiation on Cancer cells

Radiation is energy that's carried by waves or a stream of particles. Radiation works by damaging the genes (DNA) in cells. Genes control how cells grow and divide. When radiation damages the genes of cancer cells, they can't grow and divide any more. Over time, the cells die. This means radiation can be used to kill cancer cells and shrink tumors.[1]

The Cell Cycle

To understand how radiation works as a cancer treatment, it helps to know the normal life cycle of a cell. The cell cycle has 5 phases, one of which is the actual splitting of the cell. When a cell splits, or divides, into 2 cells, it's called *mitosis*. This 5-phase process is controlled by proteins known as *cyclin-dependent kinases* (CDKs). Because CDKs are so important to normal cell division, they too have a number of control mechanisms.

Steps of Cell Cycle

G_0 phase (resting stage): The cell has not yet started to divide. Cells spend much of their lives in this phase, carrying out their day-to-day body functions, not dividing or preparing to divide. Depending on the type of cell, this stage can last for a few hours or many years. When the cell gets the signal to divide, it moves into the G1 phase.

G_1 phase: The cell gets information that determines if and when it will go into the next phase. It starts making more proteins to get ready to divide. The RNA needed to copy DNA is also made in this phase. This phase lasts about 18 to 30 hours.

S phase: In the S phase, the chromosomes (which contain the genetic code or DNA) are copied so that both of the new cells to be made will have the same DNA. This phase lasts about 18 to 20 hours.

G_2 phase: More information about if and when to proceed with cell division is gathered during this phase. The G2 phase happens just before the cell starts splitting into 2 cells. It lasts from 2 to10 hours.

M phase (mitosis): In this phase, this lasts only 30 to 60 minutes, the cell actually splits into 2 new cells that are exactly the same.

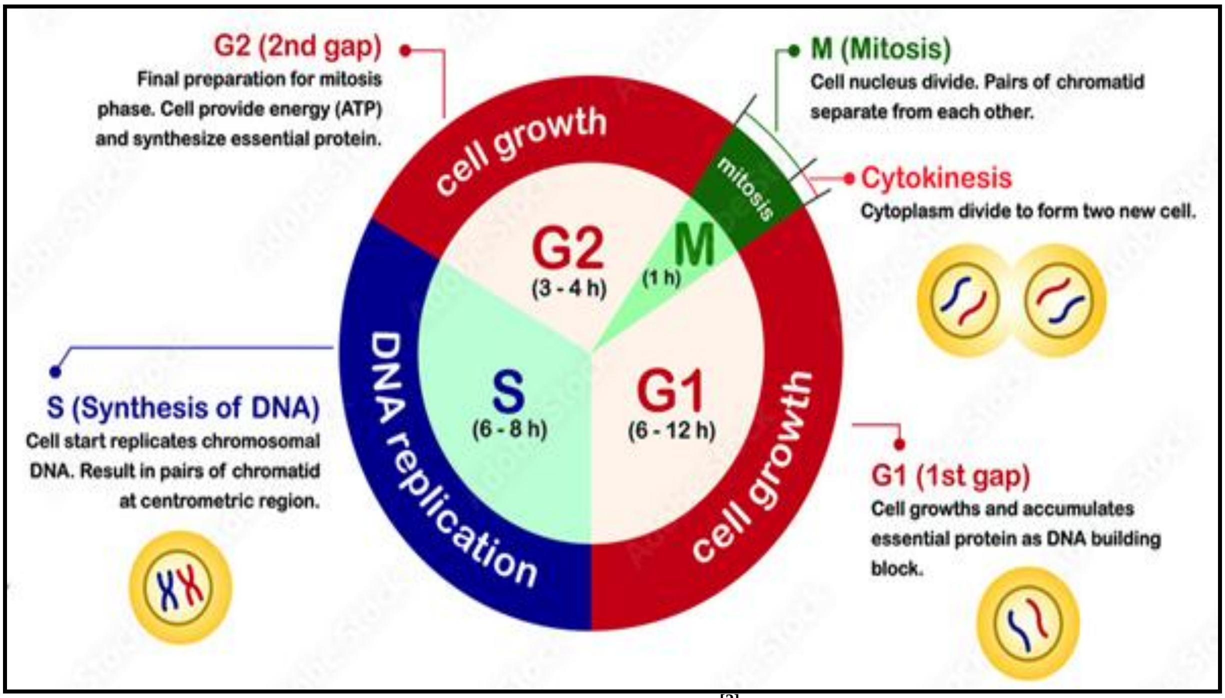

Figure 10: Cell cycle[2]

Types of Radiation used to treat Cancer

Radiation used for cancer treatment is called **ionizing radiation** because it forms ions (electrically charged particles) in the cells of the tissues it passes through. It creates ions by removing electrons from atoms and molecules. This can kill cells or change genes so the cells stop growing. Other forms of radiation such as radio waves, microwaves, and visible light waves are called **non-ionizing**. They don't have as much energy and are not able to form ions.

Ionizing radiation can be sorted into 2 major types.

- **Photon radiation** (x-rays and gamma rays)
- **Particle radiation** (such as electrons, protons, neutrons, carbon ions, alpha particles, and beta particles)

Photon Radiation: A high-energy **photon beam** is by far the most common form of radiation used for cancer treatment. It is the same type of radiation that is used in x-ray machines, and comes from a radioactive source such as cobalt, cesium, or a machine called a *linear accelerator* (linac, for short). Photon beams of energy affect the cells along their path as they go through the body to get to the cancer, pass through the cancer, and then exit the body.

Particle Radiation

Electron beams or **particle beams** are also produced by a linear accelerator. Electrons are negatively charged parts of atoms. They have a low energy level and don't penetrate deeply into the body, so this type of radiation is used most often to treat the skin, as well as tumors and lymph nodes that are close to the surface of the body.

Proton beams are a form of particle beam radiation. Protons are positively charged parts of atoms. They release their energy only after traveling a certain distance and cause little damage to the tissues they pass through. This makes them very good at killing cells at the end of their path. So, proton beams are thought to be able to deliver more radiation to the cancer while doing less damage to nearby normal issues. Proton beam radiation therapy is used routinely for certain types of cancer, but still need more study in treating others. It requires highly specialized equipment and is not widely available. Some of the techniques used in proton treatment can also expose the patient to neutrons (see below).

Neutron beams are used for some cancers of the head, neck, and prostate and for certain inoperable tumors. A neutron is a particle in many atoms that has no charge. Neutron beam radiation can sometimes help when other forms of radiation therapy don't work. Few facilities in the United States offer it, and use has declined partly because it can be difficult to target the beams effectively. Because neutrons can damage DNA more than photons, effects on normal tissue can be more severe.

Carbon ion radiation can be helpful in treating cancers that don't usually respond well to radiation (called *radioresistant* cancers). It's also called *heavy ion radiation* because it uses a particle that's heavier than a proton or neutron. The particle is part of the carbon atom, which itself contains protons, neutrons, and electrons. Because it's so heavy, it can do more damage to the target cell than other types of radiation. As with protons, the beam of carbon ions can be adjusted to do the most damage to the cancer cells at the end of its path. But the effects on nearby normal tissue can be more severe. This type of radiation is only available in a few centers in the world. **Alpha and beta particles** are mainly produced by special radioactive substances that may be injected, swallowed, or put into the body. They're most often used in imaging tests, but can be helpful in treating cancer.

Objectives of Radiation Therapy

Most types of radiation are considered *local* treatments because the radiation is aimed at a specific area of the body (where there's a tumor). Only cells in that area are affected. Most forms of radiation therapy can't reach all parts of the body, which means they're not helpful in treating cancer that has spread to many distant areas. Radiation is used to treat cancer in several ways.

To cure or shrink early stage cancer-

Some cancers are very sensitive to radiation. Radiation may be used by itself in these cases to make the cancer shrink or disappear completely. Sometimes, a few cycles of chemotherapy are given first. For other cancers, radiation may be used before surgery (as *pre- operative* or *neoadjuvant therapy*) to shrink the tumor, or after surgery to help prevent the cancer from coming back (this is called *adjuvant therapy*). For certain cancers that can be cured either by radiation or by surgery, radiation may be preferred because it can sometimes preserve the organ's function (such as that of the larynx or the anus). In treating some types of cancer, radiation may also be used along with chemotherapy (chemo). This is because certain chemo drugs act as *radiosensitizers;* they make the cancer cells more sensitive to radiation. These drugs make the radiation work better. The drawback of giving chemo and radiation together is that side effects tend to be worse. When radiation is used along with other forms of therapy, the treatment is planned by the surgeon, medical oncologist, and radiation oncologist, as well as the patient.

To stop cancer from recurring somewhere else- If a type of cancer is known to spread to a certain area, doctors often assume that a few cancer cells might already have spread there, even when imaging scans (such as CT or MRI) show no tumors. That area may be treated to keep these cells from growing into tumors. For example, people with some types of lung cancer may get *preventive* (or *prophylactic*) *radiation* to the head because this type of cancer often spreads to the brain. Sometimes, radiation to prevent future cancer can be given at the same time that radiation is given to treat existing cancer, especially if the prevention area is close to the tumor itself.

To treat symptoms caused by advanced cancer- Sometimes cancer spreads too far to be cured. But even some of these tumors can still be treated to make them smaller so that the person can feel better. Radiation might help relieve symptoms such as pain, trouble swallowing or breathing, or bowel blockages that can be caused by advanced cancer. This is often called *palliative radiation*.

Treatment of bone pain: Strontium-89 (Metastron®), samarium-153 (Quadramet®), and radium-223 (Xofigo®) are radiopharmaceuticals that can be used for tumors that have spread to the bones (bone metastases). Other drugs are also being studied. These medicines are given in veins (intravenously or IV), so that they go into the blood circulation. They travel through the body and build up in the areas of the bone where there is cancer. The radiation they give off then kills cancer cells and eases the pain caused by bone metastases. For cancer that has already spread to several bones, this approach can be better than trying to aim external beam radiation at each affected bone. These drugs may be used along with external beam radiation which is aimed at the most painful bone metastases. This combined approach has helped many men with prostate cancer, but it has not been studied as much for use in other cancers. Some people notice more bone pain for the first couple of days after treatment, but this isn't common. These drugs can also lower blood cell counts, especially white blood cells (which can increase the risk of infection) and platelets (which can raise the risk of bruising or bleeding).

Treatment of thyroid cancer: The thyroid gland absorbs nearly all of the iodine in the blood. Because of this, *radioactive iodine* (also called *radioiodine* or *iodine-131*) can be used to destroy the thyroid gland and thyroid cancer with little effect on the rest of the body. This treatment is often used after thyroid cancer surgery to destroy any thyroid cells left behind. It's also used to treat some types of thyroid cancer that spread to lymph nodes and other parts of the body.

Phosphorus-32: This form of phosphorus (also known as *P-32* or *chromic phosphate P- 32*) is put inside brain tumors that are cystic (hollow) to kill the tumor without hurting the healthy parts of the brain. In the past, P-32 was given into a vein (as an IV) as a common treatment for a blood disease called *polycythemia vera*. P- 32 was also placed inside the abdomen (belly) as a treatment for ovarian cancer. It's rarely used in these ways today, because there are better drugs with fewer side effects.

Radio-labeled antibodies: Monoclonal antibodies are man-made versions of immune system proteins that attack only a specific molecular target on certain cancer cells. Scientists have learned how to pair these antibodies with radioactive atoms. When put into the bloodstream, the antibodies act as homing devices. They attach only to their target, bringing tiny packets of radiation directly to the cancer. Radio-labeled antibodies are used to treat some non-Hodgkin lymphomas, especially those that don't respond to other treatments.

Risks Associated with Radiation Therapy

The link between radiation and cancer was confirmed many years ago through studies of the survivors of the atomic bombs in Japan, the exposures of workers in certain jobs, and patients treated with radiation therapy for cancer and other diseases. Some cases of leukemia are related to past radiation exposure. Most develop within a few years of exposure, with the risk peaking at 5 to 9 years, and then slowly declining. Other types of cancer that develop after radiation exposure have been found to take much longer to show up. These are solid tumor cancers, like breast or lung cancer. Most are not seen for at least 10 years after radiation exposure, and some are diagnosed even more than 15 years later. Radiation therapy techniques have steadily improved over the last few decades. Treatments now target the cancers more precisely, and more is known about setting radiation doses. These advances are expected to reduce the number of secondary cancers that result from radiation therapy. Overall, the risk of second cancers is low and must be weighed against the benefits gained with radiation treatments.

Common physical side effects of radiation therapy include[3]

Skin changes: Some people who receive radiation therapy experience dryness, itching, blistering, or peeling. These side effects depend on which part of the body received radiation therapy and other factors. Skin changes from radiation therapy usually go away a few weeks after treatment ends. If skin damage becomes a serious problem, your doctor may change your treatment plan. Lotion may help with skin changes, but be sure to check with your nurse or other health care team about which cream they recommend and when to apply it. It is also best to protect affected skin from the sun. Learn more about skin-related side effects.

Fatigue: Fatigue is a term used to describe feeling tired or exhausted almost all the time. Many patients experience fatigue. Your level of fatigue often depends on your treatment plan. For example, radiation therapy combined with chemotherapy may result in more fatigue. Learn how to cope with fatigue.

Long-Term Side Effects: Most side effects go away after treatment. But some continue, come back, or develop later. These are called long-term or late effects. One possible late effect is the development of a second cancer. This is a new type of cancer that develops because of the original cancer treatment. The risk of this late effect is low. And the risk is often smaller than the benefit of treating the first cancer.

What are site-specific side effects of radiation therapy?
Some side effects depend on the type and location of where radiation therapy is directed at on the body.

Head and Neck: Radiation therapy aimed at a person's head or neck may cause these side effects:

- Dry mouth
- Mouth and gum sores
- Difficulty swallowing
- Stiffness in the jaw
- Nausea
- Hair loss
- A type of swelling called lymphedema
- Tooth decay

Chest: Radiation therapy aimed at the chest may cause these side effects.

- Difficulty swallowing
- Shortness of breath
- Breast or nipple soreness
- Shoulder stiffness
- Cough, fever, and fullness of the chest, known as radiation pneumonitis. This happens between 2 weeks and 6 months after radiation therapy.
- Radiation fibrosis, which causes permanent lung scars from untreated radiation pneumonitis. The radiation oncologist knows how to lower the risk of fibrosis.

Stomach and Abdomen: Radiation therapy aimed at the stomach or abdomen may cause these side effects.

- Loss of appetite
- Nausea and vomiting
- Bowel cramping
- Loose stool or diarrhea
  These symptoms will likely go away after treatment. During treatment, your doctor can prescribe medicine to manage these side effects. Making changes to your diet may also reduce symptoms. It may be helpful to talk with an oncology dietitian.

Pelvis. Radiation therapy aimed at the pelvis may cause these side effects.

- Loose stool or diarrhea
- Rectal bleeding
- Incontinence, which is when a person is not able to control his or her bladder
- Bladder irritation
- Sexual problems for men, such as erectile dysfunction, which is the inability to get or maintain an erection
- Lowered sperm counts and reduced sperm activity. This can occur from radiation therapy to the testicles (testes) or prostate gland. It can affect your ability to have children. Learn about ways to preserve fertility for men.
- Changes in menstruation, such as having menstruation stop
- Symptoms of menopause, such as vaginal itching, burning, dryness, and other changes to sexual health for women
- If both ovaries receive radiation therapy, you may experience infertility. Learn about ways to preserve fertility for women.

CONCLUSION

An understanding of the principles of radionuclide production extends translational knowledge to the application of diagnostic and therapeutic nuclear medicine procedures. The production processes are not generally complex and are important to broader applications in research. Nowadays, the branch of nuclear pharmacy is directed to introduce new radioactive pharmaceutical agents that will be important and effective in the treatment of cancer. The growth in the field of radiopharmaceuticals is important to help millions of patients suffering from tumors all over the world.

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