FABAD J. Pharm. Sci., 46, 1, 93-104, 2021

REVIEW ARTICLES

Therapeutic Applications of Radiopharmaceuticals: An Overview

Erol AKGUN[*], Emre OZGENC[**o], Evren GUNDOGDU[***]

Overview of Radiopharmaceuticals Used in Treatment

SUMMARY

Radiopharmaceuticals are radioactive medications (radioisotopes) and are composed of radionuclidic and pharmaceutical parts. Recently, the use of radiopharmaceuticals as diagnostic and therapeutic agents is increasing. Several approaches have been employed to develop therapeutic radiopharmaceuticals. Therapeutic radiopharmaceuticals have essential roles in nuclear medicine administrations. Today, various diseases such as thyroid cancer, metastatic bone cancer, neuroendocrine tumors, and myeloproliferative can be treated with radioimmunotherapy. These treatments provide convenience in multiple ways and can be advantageous compared to other treatment methods. In this review, current radiopharmaceuticals and their usage in different disease treatments are summarized by providing fine details. Also, the definition of theranostics is summed up. In conclusion, this review can be beneficial for scientists who work in this area.

Key Words: *Radiopharmaceutical, Treatment, Nuclear Medicine, Radionuclide, Radioimmunotherapy, Theranostics.*

Tedavide Kullanılan Radyofarmasötiklere Genel Bakış

ÖZ

Radyofarmasötikler, radyonüklidik ve farmasötik kısımlardan oluşan radyoaktif ilaçlardır. Son zamanlarda, radyofarmasötiklerin teşhis ve tedavideki kullanımı artmaktadır. Terapötik radyofarmasötiklerin geliştirilmesi için çeşitli yaklaşımlar kullanılmıştır. Terapötik radyofarmasötiklerin nükleer tıp uygulamalarında önemli rolleri vardır. Günümüzde radyoimmünoterapi ile; tiroid kanseri, metastatik kemik kanseri, nöroendokrin tümörler ve miyeloproliferatif gibi çeşitli hastalıklar tedavi edilebilmektedir. Bu tedaviler çeşitli şekillerde kolaylık sağlar ve diğer tedavi yöntemlerine kıyasla avantajlı olabilir. Bu derlemede, mevcut radyofarmasötikler ve çeşitli hastalıkların tedavisinde kullanımları özel ayrıntılar verilerek özetlenmiştir. Ayrıca, "teranostik" tanımı özetlenmiştir. Sonuç olarak, bu derleme bu alanda çalışan bilim insanları için faydalı olabilir.

Anahtar kelimeler: *Radyofarmasötik, Tedavi, Nükleer Tıp, Radyonüklit, Radyoimmunoterapi, Teranostik.*

Received: 7.07.2020
Revised: 20.09.2020
Accepted: 27.10.2020

[**] ORCID NO: 0000-0002-7586-8520, Department of Radiopharmacy, Faculty of Pharmacy, Ege University, Izmir, Turkey
[***] ORCID NO: 0000-0003-2111-101X, Department of Radiopharmacy, Faculty of Pharmacy, Ege University, Izmir, Turkey

[*] Corresponding Author: Emre ÖZGENÇ
Phone: 232 311 3282; e-mail: emre.ozgenc@ege.edu.tr

INTRODUCTION

Radiation is the condition of atoms breaking down spontaneously by emitting energy to make them more stable. The heavy nucleus of atoms is unstable because of their high energy amount and try to become stable to abandon this situation. This situation is called radioactivity or radioactive degradation (Asikoglu et al., 2017). Radioactivity is substantial in radiopharmacy studies. Radiopharmacy is a significant part of pharmacy, concerned with the preparation, distribution, and administration of radioactive drugs. The development of radiopharmacy has also been begun with the discovery of radiation (Asikoglu et al., 2017; Kovan, 2016; Ozer, 2004).

Radiopharmaceuticals are drugs and used for the diagnosis and treatment of diseases (Silindir Gunay, 2020). They can be administered to patients safely. In nuclear medicine applications, 95% of radiopharmaceuticals are used for diagnosis, and 5% for treatment. The radiopharmaceuticals used in diagnosis emit gamma (γ)-ray, and the radiopharmaceuticals used in treatment emit alpha (α) and beta (ß) particles (Asikoglu et al., 2017; Henkin et al., 2006). The main features of radiopharmaceuticals used in diagnosis or treatment are shown in Table 1.

Table 1. The features of radiopharmaceuticals used in diagnosis or treatment (Asikoglu et al., 2017).

	Diagnosis	**Treatment**
Radioisotopes	These should emit γ and β^+ rays	These should emit α and $ß^-$ rays
Energy	150 KeV on average	Medium/high energy (>1MeV)
Effective half life	1,5 x test time	Hour/day
Localization	High in the target organ	High in the target organ
Radiation dose	Low dose, high efficiency	Effective dose
Finding	Easy and cheap	Easy and cheap
Quality control	Easy	Easy

Nuclear medicine is an area of medicine and has a significant role in the diagnosis, and treatment of many diseases. With nuclear medicine imaging studies, medical problems can be identified at an early stage and treatment can also be provided using radiopharmaceuticals. In nuclear medicine, radiopharmaceuticals show therapeutic efficiency by destroying the target cells in the tissue with radiation (Kovan, 2016; Sivri et al., 2004). Radiopharmaceuticals used for diagnosis and treatment in nuclear medicine are shown in Table 2.

Table 2. Radiopharmaceuticals for diagnostic and therapeutic applications (Asikoglu et al., 2017; Yordanova et al., 2017).

Diagnosis of Diseases with Radiopharmaceuticals	Treatment of Diseases with Radiopharmaceuticals
Sodium Fluoride (^{18}F) Solution for Injection	I-131
(^{18}F)-Fluoro-2-Deoxy-D-Glucose (^{18}F) FDG) Solution for Injection	Phosphorus-32 (P-32),
(^{18}F) Florotimidin Çözeltisi.	Strontium Chloride (Sr-89),
^{68}Ga-PSMA	Rhenium Diphosphonate (Re-186)
^{68}Ga-DOTATATE	Smarium-153 (Sa-153),
Radiopharmaceuticals prepared with technetium-99m	Tin-117m (Sn-117m)
Xenon-133	Lu-177 Dotatate
Thallium-201 Chloride	I-131-tositumomab
Iodine-131 sodium iodide	Yttrium-90 (Y-90)-ibritumomab tiuxetan
Indium-111 labeled leukocytes	I-131-metaiodobenzylguanidine (MIBG)
Indium-111 octreskan	Erbium citrate colloid (Er169)

1.1. Diagnosis of Diseases with Radiopharmaceuticals

Radiopharmaceuticals that emit gamma rays are used in nuclear medicine to diagnose disease and determine the condition and function of specific tissue and organ (Gundogdu et al., 2018). There are two standard methods to diagnose the disease with radiopharmaceuticals:

Non-image diagnostic applications: The radiopharmaceutical is reached to the desired organ/tissue, and radioactivity is counted from outside. The radioactivity calculation in the organ can be calculated with the Medical Internal Radiation Dose (MIRD), and the body surface area can be calculated using Monte Carlo methods (Kovan, 2016).

Image diagnostic applications: The radiopharmaceutical is reached to desired organ/tissue and the organ/tissue is imaged by various imaging systems such as gamma cameras, single-photon emission computed tomography (SPECT), Positron Emission Tomography (PET), SPECT/CT, and PET/CT hybrid systems (Gundogdu et al., 2018).

1.2. Treatment of Diseases with Radiopharmaceuticals

Radiopharmaceuticals that emit alpha and beta rays are administered in many nuclear medicine treatment studies. The radiopharmaceuticals are given to the patient and kept in the target tissue/organ. They destroy diseased tissue and provide the treatment. In this way, near/healthy tissues are exposed to dose as low as possible and targeted therapy occurs (Kovan, 2016; Sivri et al., 2004). The properties of the radionuclides used for radionuclide therapy are given in Table 3. Elemental, metabolic, pharmaceutical agents, antibodies, bone imaging chelates, bioreducing agents, labeled cells, liposomes, microspheres, nanoparticles and niosomes are radiolabeled with radionuclides suitable for the treatment of diseases. These have some advantages:

- They are non-invasive treatment,
- They show medium and long-term low side effects,
- These agents are useful because they can be targeted.
- The dose in normal tissue is low because these agents can be absorbed in desired tissues (Sivri et al., 2004).

There are many radiopharmaceuticals that are used in the treatment of some diseases. The samples of radiopharmaceuticals are summarized below.

Classification of Treatments Using Radiopharmaceutics:

1. Radioactive iodine therapy in thyroid diseases
2. Radiopharmaceutical treatment in metastatic bone pain
3. Radionuclidic therapy in neuroendocrine tumors
4. Treatment with labeled antibody
5. Intra-cavitary radiocolloid therapy
6. Radiation synovectomy
7. Radionuclidic therapy in myeloproliferative diseases
8. Intra-arterial radionuclide therapy by radiolabeled microspheres

1.2.1 Iodine-131 Treatment in Thyroid Diseases

The treatment of benign and malignant diseases of the thyroid can be done with Iodine-131 (I-131). Radioiodine therapy has been used for a long time. In treating diseases such as hyperthyroidism, I-131 radionuclide settles in the thyroid tissue. It destroys the follicle cells with the beta particles it emits and stops the growth and activities of the thyroid cells. In this case, it returns the functions of the overactive thyroid gland to normal (Mumtaz et al., 2009). In malignant diseases such as thyroid cancer, radioactive iodine therapy can also be applied to remove residual thyroid gland residues after thyroid surgery and treatment of the spread of thyroid cancers in the body. Since the dose of radioactive iodine preferred in the treatment of thyroid cancers is higher than the iodine dose in the treatment of hyperthyroidism, the patient should sleep in a room specially prepared for radioiodine

treatment to prevent radiation to the environment. The drugs and diet used before the treatment should be adjusted within the framework of certain rules (Luster et al., 2008). The half-life of I-131 is eight days, and beta energy is 0.61 MeV. I-131 shows activity in the treatment of thyrotoxicosis, hyperthyroidism, thyroid cancer. It affects the formation of the thyroid hormone and creates atrophy in the tissue. Thus, the thyroid gland becomes smaller, and thyroid hormone level decreases. As a result, reduced cell proliferation occurs (Onsel, 1999; Adalet et al., 2012). The patients should be on a low iodine diet for at least a week and avoid iodized salt, milk, dairy products, eggs, fish, seafood, and red meats under the treatment of I-131. Tincture of iodine and similar antiseptic agents should not be used for two weeks after the treatment. If patients have dentures, radioiodine should be drunk after the removal of dentures. Food should not be eaten for an hour after the administration of I-131. Radioactive iodine therapy cannot be used in pregnant women. I-131 biodistribution is performed by the urinary system, stomach, salivary glands. Saliva and urine flow can be increased by water, and I-131 level can be reduced. Gum and lemon slices should be chewed to prevent saliva accumulation (Sivri et al., 2004).

I-131 has some side effects: Radiation thyroiditis, neurological complications (edema and related neurological complications), sialadenitis (painful, sensitive and impaired function of salivary glands, taste disturbance and dry mouth), gastrointestinal complications, hematological complications. Late side effects include amenorrhea, testicular damage and decreased sperm, bone marrow suppression, and lung fibrosis (Handelsman et al., 1983; Onsel, 1999; Raymond et al., 1989)

1.2.2. Radiopharmaceutical Treatment in Metastatic Bone Pain

Pain is the most critical symptom in approximately 70% of patients with advanced cancer, and interventions against pain management are mostly inadequate. With radiation therapy, bone pain caused by metastatic cancer can be controlled non-invasively, and functional status is improved. The emergence of new painful metastases can also be prevented or delayed (Liepe et al., 2005). Ideal radiopharmaceuticals used in pain palliative treatment should be retained explicitly in bone and quickly eliminated from soft tissues. The biological half-life must react with the retained bone and must be long enough to irradiate the surrounding tumor before a significant breakthrough occurs (Guerra Liberal et al., 2016). P-32, Sr-89, Re-186, Sa-153, Sn-117m are radiopharmaceuticals and used for palliative treatment of metastatic cancer pain. For example, Sr-89; is effective in patients with skeletal metastases and more beneficial than drugs such as chemotherapeutic, hormones, and analgesics. The initial dose of therapeutic activity may vary depending on the radionuclide used. Pain status may increase temporarily at the beginning of treatment, and bone marrow suppression may occur within 4-6 weeks after radiopharmaceuticals administration. When radiopharmaceuticals are used in combination with chemotherapy or local radiotherapy, it increases the effectiveness of the treatment. (Sivri et al., 2004; Paes et al., 2010; Adalet et al., 2012; Lewin, 2018).

1.2.3. Radionuclidic therapy in neuro-endocrine tumors

Neuroendocrine tumors create complicated clinical pictures. These tumors are heterogeneous group tumors. Neuroendocrine tumors develop in the gastrointestinal and lungs, but about 70% of these originate from the gastroenteropancreatic system. Their incidence has been reported as 5.25 per 100,000 (Ozkan, 2019). Neuroendocrine tumors can synthesize, store and secrete neuroamines and peptides. Functional neuroendocrine tumors or dysfunctional neuroendocrine tumors, known as carcinoid syndrome, can lead to symptoms such as flushing, diarrhea, and right heart failure (Kaltsas et al., 2004). Clinical cases caused by functional neuroendocrine tumors have been treated with somatostatin analogs (SSA) for many years. However, with the progression of the disease, patient management becomes more complex, and the choice of alternative therapies is important for both survival and quality of life. (Kamp et al., 2013).

Neuroendocrine tumors, which are considered to be a slow disease, are very aggressive after they become metastatic, and especially liver metastases determine survival. Although surgical resection is recommended as a treatment option in these patient groups, many patients are not suitable for this treatment method, and hepatic embolization methods are frequently used in this patient group. Besides, peptide receptor radionuclide treatments have positive results in combination with systemic therapies used in patients with neuroendocrine tumors, and serious toxic effects are not encountered (Ozkan, 2019). Neuroendocrine cancers are cancers that are generally seen in the intestine, stomach, pancreas, and lung systems. Lu-177 dotatate and I-131-metaiodobenzylguanidine (MIBG) are currently used in the treatment of neuroendocrine cancers.

1.2.3.1. I-131-MIBG Treatment

I-131-MIBG is highly effective in pheochromocytoma and neuroblastoma. Also, I-131-MIBG is less effective in paraganglioma, carcinoid tumors, and medullary thyroid cancer. This treatment is not preferred in pregnant patients. Renal functions and bone marrow reserve should be sufficient for the success of the treatment.

Radiation affects the cells by using ß-rays emitted from the I-131 MIBG being held by neighboring cells. Therefore, isolated cells are exposed to radiation less than macroscopic tumors and cell clumps. As a result, smaller tumors are exposed to radiation less, and the chance of treatment is less (Grünwald et al., 2010; Adalet et al., 2012).

1.2.3.2. Lutetium-177 Dotatate Treatment

Lutetium-177 Dotatate is a prescribed radiopharmaceutical used in the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This radiopharmaceutical concentrates on the tumor structure and treats the cancer with beta rays. This form of treatment is applied 4 or 5 times with an average of two months' periods. In this treatment, critical organs such as the kidney, bone marrow, and liver are exposed to some dosage. The radiation dose in the target organ is adjusted according to the maximum treatment dose of the treatment and the patient's weight (Kovan, 2016).

1.2.4. Treatment with Labeled Antibody

Radio-labeled antibodies were first studied for tumor imaging, but with the use of F-18-FDG in positron emission tomography, radio-labeled antibodies are no longer used for tumor detection. Later studies have shown that radiolabeled antibodies are useful in treating lymphoma (Barbet et al., 2009). Tositumomab, known as anti-B1, is a monoclonal antibody with an affinity for the CD20 antigen expressed on normal B-lymphocytes. CD20 is described in the majority of B cell lymphomas (Press et al., 2001). This antibody inhibits tumor growth in both animal models and humans (Buchsbaum et al., 1992). Tositumomab was radiolabeled with antibody I-131 (Bexxar), and B cell Non-Hodgkins was used for treatment and was approved by the FDA. Tositumomab can inhibit tumor growth in animal models and humans, but it was not developed as a human-mouse chimeric antibody. The antibody is prepared from serum-free hybridoma supernatants. It is radiolabeled by the method of oxidation of radioactive iodine with iodogen. It is commercially available, and the I-131 radiolabelled tositumomab solution contains additives (Providon, maltose, and ascorbic acid) to limit radiolysis (Cheson, 2003; Press et al., 2001). Another FDA-approved radiopharmaceutical used for B-cell Non-Hodgkins therapy is Yttrium-90-ibritumomab (Zevalin). Ibritumomab is a murine IgG1a kappa antibody and is used to treat lymphomas (Barbet et al., 2009). Yttrium-90 is a pure beta emitter, so problems caused by high-energy gamma rays emitted by iodine-131 do not arise. However, since Y-90 does not emit gamma rays, gamma imaging, and subsequent dosimetry calculations cannot be made. For this reason, indium-111 (In-111) is used with the Y-90 as it allows pre-treatment imaging for dosimetry evaluation and patient-specific dosing. In-111-ibritumomab tiuxetan and Y-90-ibritumomab tiuxetan are used to treat relapsed or refractory low-grade, follicular, or transformed B-cell NHL patients,

including follicular patients resistant to rituximab (Witzig et al., 2002).

1.2.5. Intra-cavitary radiocolloid therapy

Intracavitary radiation therapy for brain tumors using beta-emitting radionuclides emerged 50 years ago. Phosphate-32 (P-32), Y-90, and Rhenium-186 (Re-186) are mostly used in cystic craniopharyngiomas. These radionuclides are placed stereotactically, and since this method is effective, it is also a minimally invasive technique, so it is very beneficial for patient compliance. (Monaco et al., 2015). Treatment management of patients with craniopharyngioma should be aimed at preserving the quality of life and extending the life span and controlling the tumor. It is the first preferred method for patients when surgical procedures are possible. However, the need for removal of the maximal tumor in surgical operations causes potential surgical risks such as hypothalamic dysfunction, hypopituitarism and vision loss. It has been reported that craniopharyngiomas are generally involved in critical structures such as the optic apparatus, hypothalamus, and pituitary stalk. When complete resection is not possible, other treatment modalities are needed. (Niranjan et al., 2010). Intracavitary radiation therapy is one of these methods. Intracavitary radiation therapy is performed using radionuclides P-32, Y-90, and Re-186. Both P-32 and Y-90 are pure beta particle emitting isotopes made in colloidal suspensions, Re-186 having both beta and gamma emission. Also, it has also been reported that Re-186 preparations are less dense and could potentially protrude beyond the cyst wall. Since pure beta-emitting radionuclides do not emit gamma rays, they provide ease of use in terms of radioprotection for the patient environment. The short penetration of beta particles prevents the healthy cells of the patient from receiving unnecessary radiation. (Backlund et al., 1989; Julow et al., 1985). Ideally, the radionuclide is desired to be a pure high energy beta emitter. The efficiency of both beta and gamma-emitting radionuclides is limited by the gamma rays they emit. P-32 has lower beta energy than Y-90 and has a shorter penetration and a longer half-life. The shorter penetration allows healthy cells to be exposed to less radioactivity in treatment. Besides, the fact that the radionuclide has a longer half-life enables tumor cells to be exposed to radioactivity for a longer time (Blackburn et al., 1999).

1.2.6. Radiation Synovectomy Treatment

Radiation synovectomy therapy is a form of treatment performed by intraarticular injection of beta-emitting radionuclides. Synovial cells are irradiated with beta radiation, reducing cell proliferation and causing cell destruction. In different types of arthritis and osteoarthritis, synovitis is the leading cause of pain and discomfort. Therefore, the destruction of synovial cells by the radiosynovectomy method is an option when surgical procedures cannot be used. (Karavida et al., 2010). Surgical synovectomy requires general anesthesia, reduces joint movement, requires a long hospital stay, and increases the risk of infection. While surgical synovectomy is not preferred primarily, radiation synovectomy is preferred (Kavakli et al., 2002; Polat, 2010). Diseases in which radiation synovectomy is indicated; rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, synovitis, osteoarthritis, villonodular synovitis, and hemophilic synovitis caused by inflammation of the synovial membrane (Adalet et al., 2012; Schneider et al., 2005). The most widely used radionuclides Y-90, Re-186, Erbium-169 (Er-169), and P-32 are the most commonly used in nuclear medicine to treat radiosynovectomy. According to the density of the synovial cells, the radionuclide with the appropriate physical half-life is selected. Besides, the average tissue penetration of the emitted particulate radiation is an essential parameter for radionuclide selection. The particle size of the radionuclides used according to the common area to be treated is also essential. The biodegradability of the radionuclides injected into synovial cells, and the irreversible binding of the radionuclide to them are too crucial in the selection of radiopharmaceuticals for radionuclide treatment. The smaller the joint, the shorter the penetration of the emitted beta particles should be (Farahati et al., 2002).

Synovioortesis is a non-surgical method of synovectomy, applied by injection of a radioactive or chemical substance into the knuckle. However, radiation synovectomy is a good option that is much more effective than chemical synovectomy. The chemical synovectomy is an excruciating procedure, and that should be repeated frequently. Chemical synovectomy method is preferred only in places where reach to radionuclide agents is insufficient (Molho et al., 1999; Haklar, 2005; Polat, 2010). The basic principle of radiation synovectomy is the injection of radiopharmaceuticals into the knuckle during a specific period. The source of enzymes that cause cartilage destruction and lead to knuckle pathology is secreted synovial tissue and fluid. For this reason, fibrosis of this region is the primary effect in treatment. Less joint damage is in line with good results. Radioisotope synovectomy can be preferred in treating chronic hypertrophic synovitis with recurrent hemarthrosis that non-response to hematological treatment, pigmented villonodular synovitis, osteoarthritis (Knapp et al., 1999; Sivri et al., 2004; Polat, 2010).

Sterile conditions should be provided during injection, and the physician should be sure that the injector is in the knuckle cavity. Generally, scope control is required during the application, but it is not needed for the knee knuckle (Rodriguez-Merchan et al., 2001; Polat, 2010;).

1.2.7. Intra-arterial Radionuclide Therapy by Radiolabeled Microspheres

Hepatocellular carcinoma is the most common form of primary liver tumors. The liver is the most common organ of metastatic spread, and metastasis is seen in various forms (Ahmadzadehfar et al., 2010; Adalet et al., 2012;). In cases where surgical interventions and local treatment methods cannot be applied, intra-arterial radiomicrocure treatment is preferred. It is based on the principle of elimination by giving a high radiation dose to the tumor. The basic principle of this treatment is that tumor cells in the liver are predominantly based on feeding on the hepatic artery and healthy cells providing on the portal venous system. Y-90 microspheres are selectively directed to tumor cells, so that tumor cells are exposed to high-dose radiation. However, side effects occur very little due to radiation in healthy liver and other tissues. Also, factors that limit the treatment include absorption dose calculation and radiomicrocure distribution are not homogeneous (Adalet et al., 2012; Feryal, 2019). Y-90 is used in treatment, has a half-life of 64,1 hours, and as a result of its degradation, zirconium-90 (Zr-90) is formed with a 99,98% probability. An antineutrino is formed with a maximum energy beta-particle of 2,28 MeV. All dose of Y-90 is absorbed in the liver, and patient isolation is not required for radioprotective purposes (Gulec et al., 2007; Uliel et al., 2012; Mehmet, 2017).

1.3. Radiopharmaceuticals in Theranostics Administration

Theranostics are mainly used in the treatment of cancerous and infected areas. Thanks to its diagnostic and therapeutic properties, theranostics reduce the side effects of treatments, and increase compliance and survival rates for patients. As a result of this approach, molecular imaging is applied by combining the diagnostic and therapeutic methods with the diagnostic agent, which has the same or similar chemical structure as the therapeutic. Predictions about the response to treatment are provided. With this method, diseases can be classified according to the molecular phenotype, the biodistribution of the molecule can be observed, and the response to treatment can be monitored (Durak, 2015; Kelkar et al., 2011; Lee, 2011).

The correlation between the diagnostic and therapeutic methods can be divided into three groups. These groups are:

-Diagnostic and therapeutic molecules are the same,

-Diagnostic and therapeutic molecules are similar,

-Diagnostic and therapeutic molecules are different, but the effect mechanism of them is similar

Same Diagnostic and Therapeutic Molecules

The best example for this group is the use of I-131.

It can be used in diagnosis and therapy. Also, Indium-111 (In-111) Octreotide therapy and, In-111 Octreotide scintigraphy, I-131 MIBG therapy and I-131 MIBG scintigraphy, Lu-177 DOTA therapy, and Lu-177 DOTA scintigraphy are examples of this group (Durak, 2015; Srivastava, 2012).

Similar Diagnostic and Therapeutic Molecules

Examples for this group are imaging with Technetium-99m (Tc-99m)-MDP or Tc-99m-HDP, treatment with Re-186-HEDP, or Sm-153-EDTMP, and imaging with Ga-68-DOTA and treatment with Lu-177 or Y-90 DOTA peptides (Srivastava, 2012).

Due to the different electron configurations of radionuclides, chemical and biochemical features, molecular stability, and biological behavior of radiopharmaceuticals can differ, but similar behavior is expected for these molecules (Durak, 2015).

Different Diagnostic and Therapeutic Molecules, But Similar Effect Mechanism

The treatment with the Y-90 microsphere, imaging with Tc-99m MAA in liver cancer, can be given as the most common sample of this group. Although the molecules are entirely different from each other, the behavior is similar (Durak, 2015).

CONCLUSION

The selection of suitable radionuclides is essential in any therapeutic radiopharmaceutical development. Their nuclear emission characteristics, physical half-life, degradation properties effect in vivo pharmacokinetics, cost, and availability of the radiopharmaceuticals. Also, types of particle emission affect the distribution and pharmacokinetics of the radiopharmaceuticals. For therapeutic radiopharmaceuticals, radionuclides that degrade by α-particle, B-particle, and Auger-electron emission are commonly used in the preparation.

In this review article, information about the radiopharmaceuticals used in the treatment is given. Today, a limited number of radiopharmaceuticals are routinely used in the treatment of many diseases. In the past ten years, clinical studies have been focused on radioimmunotherapy. Studies on radiolabeled monoclonal antibodies and radiolabeled receptor binding agents are being conducted. Few studies have achieved their goal so far and are currently used in treatment. The best results have been achieved in treating lymphomas, and two FDA-approved radiopharmaceuticals are used in practice. Radiopharmaceutical science is an emerging research field that meets the clinical standards. They have an essential therapy index and high imaging ability. The scientific community examines various radionuclides, pharmaceutical agents, radiopharmaceuticals, and evaluating in vivo performance of newly developed radiopharmacauticals. Thus, great efforts are being made to develop new radiopharmaceuticals to be converted into clinical research to treat many diseases. As detailed in this review, most of the current studies focus on the diagnostic and therapeutic applications of radiopharmaceuticals. We believe that these developments will have positively affects on human life and lead to positive results in the diagnosis and therapy of patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTION STATEMENT

Developing hypothesis (Gundogdu E.) preparing the study text (Akgun E., Ozgenc E.) reviewing the text (Gundogdu E., Ozgenc E.) literature research (Akgun E., Ozgenc E.)

REFERENCES

Adalet, A. M., Unal, S. N., Turkmen, C. I. (2012). Nukleer tıp ders kitabı. Istanbul University Publications, Istanbul.

Ahmadzadehfar, H., Biersack, H. J., Ezziddin, S. (2010). Radioembolization of Liver Tumors With Yttrium-90 Microspheres. *Seminars in Nuclear Medicine*, *40*(2), 105–121. https://doi.org/10.1053/j.semnuclmed.2009.11.001

Asikoglu, M., Ilem Ozdemir, D., Atlihan Gundogdu, E. (2017). Radyofarmasi. Ege University Publications, Izmir.

Atlihan Gundogdu, E., Ozgenc, E., Ekinci, M., Ilem Ozdemir, D., Asikoglu, M. (2018). Radiopharmaceuticals Used in Imaging and Treatment in Nuclear Medicine. *Journal of Literature Pharmacy Sciences*, *7*(1), 24–34. https://doi.org/10.5336/pharmsci.2017-56434

Backlund, E. O., Axelsson, B., Bergstrand, C. G., Eriksson, A. L., Norén, G., Ribbesjö, E., Rähn, T., Schnell, P. O., Tallstedt, L., Sääf, M., Thorén, M. (1989). Treatment of craniopharyngiomas - the stereotactic approach in a ten to twenty-three years' perspective - I. Surgical, radiological and ophthalmological aspects. *Acta Neurochirurgica*, *99*(1–2), 11–19. https://doi.org/10.1007/BF01407771

Blackburn, T. P. D., Doughty, D., Plowman, P. N. (1999). Stereotactic intracavitary therapy of recurrent cystic craniopharyngioma by instillation of ^{90}yttrium. *British Journal of Neurosurgery*, *13*(4), 359–365. https://doi.org/10.1080/02688699943457

Bozkurt, M. (2017). Kolanjiyokarsinom tanısı ile karaciğer metastazlarına y-90 mikroküre tedavisi verilmiş hastalarda hepatik arter perfüzyon çalışması görüntüleri ile tedavi öncesi – tedavi sonrası bilgisayarlı tomografi ve fdg pet bt görüntüleri arasındaki ilişkinin araştırılması. Hacettepe Universitesi Tıp Fakültesi Nükleer Tıp Anabilim Dalı, Uzmanlık Tezi. Ankara, 38-42.

Buchsbaum, D. J., Wahl, R. L., Normolle, D. P., Kaminski, M. S. (1992). Therapy with Unlabeled and 131I-labeled Pan-B-Cell Monoclonal Antibodies in Nude Mice Bearing Raji Burkitt's Lymphoma Xenografts. *Cancer Research*, *52*(23), 6476-6481.

Cheson, B. D. (2003). Radioimmunotherapy of non-Hodgkin lymphomas. *American Society of Hematology*, *101*(2), 391-398. https://doi.org/10.1182/blood-2002-06-1793

Durak, H. (2015). Personalized Therapy and Theranostic Approaches in Oncology. *Nuclear Medicine Seminars*, *1*(2), 80–84. https://doi.org/10.4274/nts.2015.014

Farahati, J., Schulz, G., Wendler, J., Körber, C., Geling, M., Kenn, W., Schmeider, P., Reidemeister, C., Reiners, C. (2002). Multivariate analysis of factors influencing the effect of radiosynovectomy. *NuklearMedizin*, *41*(2), 114–119. https://doi.org/10.1055/s-0038-1625643

Feryal, C. (2019). Development of a method for determination of activity quantities of Y-90 microspheres to be administered in treatment of liver tumors by patient specific modeling and standardization of the method. *Hacettepe University Publications.*

Grünwald, F., Ezziddin, S. (2010). 131I-Metaiodo benzyl guanidine therapy of neuroblastoma and other neuroendocrine tumors. In *Seminars in Nuclear Medicine, 40*(2), 153–163. https://doi.org/10.1053/j.semnuclmed.2009.11.004

Guerra Liberal, F. D. C., Tavares, A. S., Tavares, R. S. (2016). Palliative treatment of metastatic bone pain with radiopharmaceuticals: A perspective beyond Strontium-89 and Samarium-153. In *Applied Radiation and Isotopes*, *110*, 87–99. https://doi.org/10.1016/j.apradiso.2016.01.003

Gulec, S. A., Siegel, J. A. (2007). Posttherapy radiation safety considerations in radiomicrosphere treatment with ^{90}Y-microspheres. *Journal of Nuclear Medicine*, *48*(12), 2080–2086. https://doi.org/10.2967/jnumed.107.045443

Haklar, U. (2005). Diz Ekleminde Sinovektomi. *TOTBID (Türk Ortopedi ve Travmatoloji Birliği Dernegi Dergisi*, *4*(3–4), 108–117. http://dergi.totbid.org.tr/files/4_2/6.pdf

Handelsman, D. J., Turtle, J. R. (1983). Testicular damage after radioactive iodine (I-131) therapy for thyroıd cancer. *Clinical Endocrinology*, *18*(5), 465–472. https://doi.org/10.1111/j.1365-2265.1983.tb02876.x

Henkin, R. E., Bova, D., Dillehay, G. L., Karesh, S. M., Halama, J. R., Wagner, R. H., Kim, E. E. (2006). Nuclear Medicine. *The Journal of Nuclear Medicine*, *48*(5), 846. https://doi.org/10.2967/jnumed.107.040329

Barbet, J., Bardiès, M., Bourgeois, M., Chatal, J. F., Chérel, M., Davodeau, Gestin, J. F. (2009). Radiolabeled Antibodies for Cancer Imaging and Therapy. *In Radiolabeled Antibodies for Cancer Treatment, 907*, 681–695.

Julow, J., Lányi, F., Hajda, M., Simkovics, M., Arany, I., Tóth, S., Pásztor, E. (1985). The radiotherapy of cystic craniopharyngioma with intracystic installation of ^{90}Y silicate colloid. *Acta Neurochirurgica*, *74*(3–4), 94–99. https://doi.org/10.1007/BF01418795

Kaltsas, G. A., Besser, G. M., Grossman, A. B. (2004). The diagnosis and medical management of advanced neuroendocrine tumors. *In Endocrine Reviews, 25*(3), 458–511. https://doi.org/10.1210/er.2003-0014

Kamp, K., Gumz, B., Feelders, R. A., Kwekkeboom, D. J., Kaltsas, G., Costa, F. P., De Herder, W. W. (2013). Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after 177Lu-octreotate. *Endocrine-Related Cancer*, *20*(6), 825–831. https://doi.org/10.1530/ERC-13-0254

Karavida, N., Notopoulos, A. (2010). Radiation Synovectomy: An effective alternative treatment for inflamed small joints. *Hippokratia*, *14*(1), 22–27. http://www.ncbi.nlm.nih.gov/pubmed/20411055. Erişim tarihi: 15 Şubat 2020.

Kavaklı, R., Aydogdu, S., Duman, Y., Taner, M., Memis, A., Capacı, K., Hepguler, A., Yılmaz Karapınar, D., Balkan, C. (2002). Musculoskeletal issues. *Haemophilia*, *8*(4), 469–481. https://doi.org/10.1046/j.1365-2516.2002.t01-1-00001.x

Kelkar, S. S., Reineke, T. M. (2011). Theranostics: Combining Imaging and Therapy. *Bioconjugate Chem*istry, *22*(10), 1879–1903. https://doi.org/10.1021/bc200151q

Kovan, B. (2016). 177Lu İle Nöroendokrin Tümörlerinin Tedavisinde Radyasyon Dozimetrisi. *Istanbul University Faculty of Science Institute Publications.* http://katalog.istanbul.edu.tr/client/tr_TR/default_tr/search/results?qu=Tümörler+--+Tedavi.&ps=300. Erişim tarihi: 07 Haziran 2020.

Knapp, F. F., Beets, A. L., Pinkert, J., Kropp, J., Lin, W. Y., Wang, S. Y. (1999). Rhenium radioisotopes for therapeutic radiopharmaceutical development. *Inter seminar on therapeutic applications of radiopharmaceuticals* (IAEA-SR-209).

Lee, D. Y., King, C. P. (2011). Molecular theranostics: a primer for the imaging professional. *American Journal of Roentgenology*, *197*(2), 318–324. https://doi.org/doi:10.2214/AJR.11.6797

Lewin, B. (2018). Radiopharmaceuticals Metastron (Strontium-89) and Samarium-153 (Quadramet) for Metastatic Bone Pain. *Aetna*, 0361, 1-20.

Liepe, K., Runge, R., Kotzerke, J. (2005). The benefit of bone-seeking radiopharmaceuticals in the treatment of metastatic bone pain. *Journal of Cancer Research and Clinical Oncology*, *131*(1), 60–66. https://doi.org/10.1007/s00432-004-0625-0

Luster, M., Clarke, S. E., Dietlein, M., Lassmann, M., Lind, P., Oyen, W. J. G., Tennvall, J., Bombardieri, E. (2008). Guidelines for radioiodine therapy of differentiated thyroid cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, https://doi.org/10.1007/s00259-008-0883-1

Molho, P., Verrier, P., Stieltjes, N., Schacher, J. M., Ounnoughène, N., Vassilieff, D., Menkes, C. J., & Sultan, Y. (1999). A retrospective study on chemical and radioactive synovectomy in severe haemophilia patients with recurrent haemarthrosis. *Haemophilia*, *5*(2), 115–123. https://doi.org/10.1046/j.1365-2516.1999.00287.x

Monaco, E. A., Tempel, Z., Niranjan, A., Lunsford, L. D. (2015). Intracavitary Therapy: Radioisotopes 32P, 90Y, and 186Re. *In Craniopharyngiomas: Comprehensive Diagnosis, Treatment and Outcome,* Elsevier Inc, 391–403. https://doi.org/10.1016/B978-0-12-416706-3.00024-6

Mumtaz, M., Lin, L. S., Hui, K. C., & Mohd Khir, A. S. (2009). Radioiodine I-131 for the therapy of graves' disease. *The Malaysian Journal of Medical Sciences*, *16*(1), 25–33. http://www.ncbi.nlm.nih.gov/pubmed/22589645. Erişim tarihi: 10 Ocak 2020.

Naki Sivri N., Ozer, Y. (2004). Radyonüklidik Tedavi. *Meslek İçi Sürekli Eğitim Dergisi*. *1*, 1-10

Niranjan, A., Kano, H., Mathieu, D., Kondziolka, D., Flickinger, J. C., Lunsford, L. D. (2010). Radiosurgery for craniopharyngioma. *International Journal of Radiation Oncology Biology Physics*, *78*(1), 64–71. https://doi.org/10.1016/j.ijrobp.2009.07.1693

Onsel Ç. (1999). Tiroid Kanserlerinin Tanı ve Tedavisi. *İ.Ü. Cerrahpasa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri. 1,* 49-68

Ozer, Y. (2004). Radyofarmasi, Radyofarmasötiklerin Dünü, Bugünü ve Geleceği. *Meslek İçi Sürekli Eğitim Dergisi*.

Özkan, Z. G. (2019). Radioembolization in the Treatment of Neuroendocrine Tumors. *Nuclear Medicine Seminars*, *5*(2), 152–158. https://doi.org/10.4274/nts.galenos.2019.0020

Paes, F. M., Serafini, A. N. (2010). Systemic Metabolic Radiopharmaceutical Therapy in the Treatment of Metastatic Bone Pain. *In Seminars in Nuclear Medicine, 40*(2), 89–104. https://doi.org/10.1053/j.semnuclmed.2009.10.003

Polat Kelle, A. (2010). Radyonüklid sinovektominin kronik hemofilik sinovitis tedavisindeki önemi. *Çukurova Üniversitesi Tıp Fakültesi Nükleer Anabilim Dalı.* https://silo.tips/download/radyonkld-snovektomnn-kronk-hemoflk-snovts-tedavsndek-nem. Erişim tarihi: 12 Ekim 2019.

Press, O. W., Leonard, J. P., Coiffier, B., Levy, R., Timmerman, J. (2001). Immunotherapy of Non-Hodgkin's lymphomas. In Hematology the Education Program of the American Society of Hematology. *American Society of Hematology. Education Program, 2001*(1), 221–240. American Society of Hematology. https://doi.org/10.1182/asheducation-2001.1.221

Raymond, J. P., Izembart, M., Marlıac, V., Dagousset, F., Merceron, R. E., Vulpillat, M., Vallué, G. (1989). Temporary Ovarian Failure in Thyroid Cancer Patients after Thyroid Remnant Ablation with Radioactive Iodine. *The Journal of Clinical Endocrinology & Metabolism*, *69*(1), 186–190. https://doi.org/10.1210/jcem-69-1-186

Rodriguez-Merchan, E. C., Goddard, N. J. (2001). The technique of synoviorthesis. *Haemophilia*, *7*(2), 11–15. https://doi.org/10.1046/j.1365-2516.2001.00103.x

Schneider, P., Farahati, J. R. C. (2005). Radiosynovectomy in rheumatology, orthopedics, and hemophilia. *Journal of Nuclear Medicine*, *46*(1), 48–54.

Silindir Gunay, M. (2020). The Formulation of Methylene Blue Encapsulated, Tc-99m Labeled Multifunctional Liposomes for Sentinel Lymph Node Imaging and Therapy. *Turkish Journal of Pharmaceutical Sciences*, *17*(4), 381-387.

Srivastava, S. C. (2012). Paving the way to personalized medicine: Production of some promising theragnostic radionuclides at Brookhaven national laboratory. *In Seminars in Nuclear Medicine, 42*(3), 151–163. https://doi.org/10.1053/j.semnuclmed.2011.12.004

Uliel, L., Royal, H. D., Darcy, M. D., Zuckerman, D. A., Sharma, A., Saad, N. E. (2012). From the angio suite to the γ-camera: Vascular mapping and ^{99m}Tc-MAA hepatic perfusion imaging before liver radioembolization-A comprehensive pictorial review. *Journal of Nuclear Medicine 53*(11), 1736–1747. https://doi.org/10.2967/jnumed.112.105361

Witzig, T. E., Gordon, L. I., Cabanillas, F., Czuczman, M. S., Emmanouilides, C., Joyce, R., Pohlman, B. L., Bartlett, N. L., Wiseman, G. A., Padre, N., Grillo-López, A. J., Multani, P., White, C. A. (2002). Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, *20*(10), 2453–2463. https://doi.org/10.1200/JCO.2002.11.076

Yeong, C. H., Cheng, M. Hua, K. H. (2014). Therapeutic radionuclides in nuclear medicine: Current and future prospects. *Journal of Zhejiang University: Science B, 15*(10), 845–863. https://doi.org/10.1631/jzus.B1400131

Yordanova, A., Eppard, E., Kürpig, S., Bundschuh, R. A., Schönberger, S., Gonzalez-Carmona, M., Feldmann, G., Ahmadzadehfar, H., Essler, M. (2017). Theranostics in nuclear medicine practice. *OncoTargets and Therapy*, *10*, 4821–4828. https://doi.org/10.2147/OTT.S140671.