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ROLE OF RARE EARTH ISOTOPES IN DIAGNOSTIC AND THERAPEUTIC NUCLEAR MEDICINE.

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ABSTRACT

The group of rare earth elements consists of 17 elements from La to Lu (Z = 57–71) is lanthanide (Ln). Rare earth element complexes are becoming important in the diagnosis and treatment of cancer due to its chemical, physical, magnetic and 4f electron configuration. Lanthanide's potential usefulness in these areas is growing, and this timely perspective of current applications is for cancer experts and other studies interested in the latest developments and trends in this field. Some rare earth radioisotopes have been applied in nuclear medicine because of their favorable physical and decay properties. Standards for production and distribution can be made more flexible, which will help ensure the supply of medical radioisotopes. In nuclear medicine, this article investigates the use of rare earth radioisotopes in the diagnosis and treatment of cancer.

KEYWORDS : Rare earth isotopes, Nuclear medicine,

INTRODUCTION:

Rare earth elements (REE) are applied in a huge variety of modern era, these are including 17 elements. Dysprosium (Dy), Cerium (Ce), Erbium (Er), Gadolinium (Gd), Europium (ecu), Holmium (Ho), Lutium (Lu), Lanthanum (l. a.), Neodymium (Nd), Promethium (Pm), Prasethium (Pr), Praseodymium (Pr), Samarium (Sm), Terbium (Tb), Scandium (Sc) Thulium (Tm), Yttrium(Y) and Ytterbium (Yb). There are 15 lanthanides, as well as scandium (Sc) and yttrium (Y) some of the rare earth elements. [1]

Lanthanides is another name for the elements from La to Lu. Due to their close resemblance, distinguishing one REE from some other is extremely tough, because they had been first recognized as rare earth oxides, the call "earth" was given to them. REE are regularly called a brand-new mates' "treasury of new metals".[2]

Rare earth elements had been first found as a new set of factors on the end of 18th century in Sweden (Preinfalk and Morteani 1989,Voncken,2016).As said inside the international union of pure and implemented chemistry (IUPAC),REEs are a collection of seventeen chemical elements, along with yttrium (Y),scandium (Sc) and fifteen steel elements of lanthanide collection.Because of the same geochemical behavior of Y and Sc to the lanthanides,they maybe additionally taken into consideration as REEs (McLennn and Taylor,2012, Voncken, 2016).

Those elements are in most cases found in trivalent oxidation nation,whereas europium (European) also canbe observed in divalent,whilst cerium (Ce) famous tetravalent states (Laybourne et al.,2000,Wang and Liang ,2016).[3]

REEs are often labelled into two sub-business as light rare earth factors (LREEs) and heavy rare earth factors (HREEs). The elements from La57 TO 63Eu are considered as LREEs, whereas the elements from 64Gd to 71Lu, which includes Y are categorized as HREEs. In preferred, LREEs are more considerable than HREEs (McLemore ,2015).

The biomedical programs of the rare earth elements enlarge well past their use as ordinary most cancers therapeutics and imaging sellers, and guides detailing their use have accelerated over the past 15 years. Our attitude highlights cutting edge paintings in addition to insights that could power future programs for this elegance of REEs in most cancer diagnosis, remedy and we discuss latest trends in nuclear medicine and molecular imaging and therapy procedures.

Applications in nuclear medicine:

- 43Sc(T1/2=3.9Hr) and 44Sc(T1/2=4.0Hr) can both be used in PET-CT, while 47Sc (T1/2 =3.35d) is the therapeutic radioisotope and also suitable for SPECT-CT studies. 44Sc is most advantage in terms of production and pre-clinical studies.
- **44Sc** is a promising radionuclide for PET-CT with Lu177,Y90 or 47Sc as therapeutic counterparts due to its half life (T1/2=3.92Hr) and it is also advantage for the development of PET-CT radiopharmaceuticals. [4]
- ^{90}**Y** is a high-energy pure -emitter with versatile nuclear physio chemical properties (half-life 64.1 h, E_{max} = 2.27 MeV) for therapy. Range in soft tissue up to 11 mm.
- 90Y-SIR-Spheres are used to treat unresectable metastatic hepatic tumour
- Y-90 ibritumomab tiuxetan (Zevalin) is an anti- Cd20 antibody used for the treatment of non -Hodgkin's lymphoma (NHL) [5]

commonly used during a radioembolization therapy, an internal radiation therapy.

- **La** (Lanthanum) is chemically similar to the therapeutic alpha emitter 225Ac, no isotopes of actinium or its radioactive daughters possess image able $^{+}$ emissions, 132La may acts a suitable diagnostic congener of 225Ac.And promising theragnostic properties of the 132/135 La pair for PET-CT imaging. [6]
- ^{141}Ce-DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid) is a theragnostic agent targeting metastatic skeletal lesions.

Cerium-doped lutetium orthosilicate is a fast and efficient scintillator that has been mainly used as detector material in PET-CT machine. [7]

Ce141 is an alternative radionuclide for flood field uniformity testing of gamma camera.

- **142 Pr** produces via 141Pr (n, γ) reaction by irradiation in a low-fluency reactor, 142Pr cyclotron produced, could be achievable.

142Pr due to its high β (-)-emission and low specific gamma γ-emission could not only be a therapeutic radionuclide, but also a suitable radionuclide for biodistribution studies.

Internal radiotherapy using 142Pr can be classified into two sub-categories:
1) Unsealed source therapy (UST) (2) Brachytherapy.
UST via 142Pr-HA and 142Pr-DTPA in order for radio synovectomy have been proposed. In addition, 142Pr Glass seeds and 142Pr microspheres have been utilized for interstitial brachytherapy of prostate cancer and intraarterial brachytherapy of arteriovenous malformation. **[8]**

Promethium-147 **(Pm-147)** radioactive isotope for use in nuclear batteries as well as other compact low power applications.

Promethium-149 (149Pm) is one of only three radio lanthanides that can be prepared in no carrier added concentrations. This high specific activity radio lanthanide is thus suitable for targeting limited numbers of specific receptors found on many tumor cells. Promethium-149 is a moderate energy β- emitter (1.07 MeV (95.9%)) with a half-life of 2.21 days. Pm-149 also emits a low abundance of an imageable γ ray (286 keV (3%)) that may allow in vivo tracking of the therapeutic dose. **[9]**

- **Sm-153** EDTMP is a good therapeutic choice for patients with painful bone metastases. It is effective treatment of pain relief without major secondary effects.
- The short range of the Sm-153 beta particle should be advantageous when considering the dose to normal marrow. A response rate on the order of 83% has been reported. Pain relief is generally noted within 2 weeks, with a duration of 4 to 40 weeks **[10]**
- **Eu152** Rod and Disk Sources provide a safe and convenient method of calibration and quality control of scintillation detectors and well counters. These are NIST traceable within ±5% at the 99% confidence level. **[11]**
- Gadolinium-153(**Gd153**) has a half-life of 240.4 ± 10 days and emits gamma energy with strong peaks at 41Kev and 102 keV.
- In Nuclear Medicine, it serves to calibrate the equipment needed like SPECT to make X-rays.
- It ensures that the machines work correctly to produce images of radioisotope distribution inside the patient. This isotope is produced in a nuclear reactor from europium or enriched gadolinium.
- It can also detect the loss of calcium in the hip and back bones, allowing the ability to diagnose osteoporosis.
- Attenuation correction using Gd-153-line sources or X-ray transmission sources are beneficial in Differentiating attenuation artifacts. **[12]**
- Lymphoscintigraphy imaging with Gd-153 flood source provides higher quality images when compared to Co-57 flood source images. Lymphoscintigrams with Gd-153 flood source are also associated with improved sentinel lymph node detection. **[13]**
- CERN announced that the CERN-MEDICIS facility had produced its first radioisotope, a batch of terbium (^{155}Tb), part of the ^{149,152,155,161}Tb family
- The members of this emerging quadruplet family have appealing nuclear characteristics and have the potential to do justice to the proposed theory of theranostics nuclear medicine, which amalgamates therapeutic and diagnostic radioisotopes together.
- Terbium is referred as the "*Swiss knife*" because of its four valuable radioisotopes, ^{149}Tb, ^{152}Tb, ^{155}Tb, and ^{161}Tb. Despite their lucrative nuclear properties useful in diagnosis and therapy and their evolvement as successful theragnostic pair; radionuclide therapy with terbium radionuclides is still a challenge due to their low production cross section. **[14]**
- PET-CT images of a patient with NET, scan obtained after administration of 152Tb-DOTATOC.
- 165Dy is the first RSV agent which motivated clinicians to treat refractory synovitis as a substitute to surgical intervention. Therapeutic Application of Dysprosium-165-FHMA in the Treatment of Rheumatoid Knee Effusions.
- This radionuclide has a 3.6 abundance of gamma emission at 108 keV that can be used by the gamma camera to detect a possible leak. It has a tissue penetration 5.7mm. A 1.3 Mev energy of beta emissions is suitable for therapy and an extremely short half-life of 2.3Hrs reduces the effects of potential leakage. **[15]**
- Dysprosium.165 (165Dy) can bind themselves to macro aggregates (particles of an adequate size) so that there is no radioactive spreading in the lymphatic system. Their use is expected to reduce inflammation and pain and improve the articular mobility. Radiation synovectomy (RS) using 165Dy Ferric.hydroxide causes no significant radiation burden to most patients as indicated by the absence of adverse changes in levels of biomarkers of cytogenetic damage and a low incidence of leakage.
- Holmium-165 has a natural abundance of 100%, the only by product is metastable holmium-166 and Ho166 labelled microspheres for liver malignancies, Ho166 -labelled chitosan for hepatocellular carcinoma and Ho166-DOTMP for bone metastases. [16]
- 169Er (Erbium citrate colloid was firstly suggested as therapeutical agent for radiosynoviorthesis for finger joints.

169Er decays under emission of beta particles to stable (169Tm) thulium.It has a physical half life of 9.5 days and the maximum energy of the beta particles is 0.34Mev**[17]**.

- 170 Tm (T1/2 =128.4 days) E beta(max) =968 keV, E(gamma)=84 keV (3.26%) based radio pharmaceutical for bone pain palliation could offer significant advantages over that of (89) Sr.
- 170Tm-EDTMP could be explored as a cost-effective alternative to (89) SrCl2.[**18**]
- Ytterbium (Yb) is a soft silvery metallic element, is found in the minerals gadolinite, monazite, and xenotime. The production of Lu- 177 is through indirect process using the stable isotope Yb-176. Neutron radiation of Yb-176 results in the production of Yb-177, which is converted to Lu-177 through the -decay with a half-life 1.9 hour.
- In this indirect process, it is easy to separate Lu-177 from Yb- 176 due to the chemical difference between Yb and Lu. Therefore, it is possible to create a therapeutic radioisotope Lu-177, which is carrier-free, meaning that it does not contain any non-radioactive isotope.
- With this reason, it is preferred that we choose indirect process using Yb-176 to produce Lu-177[**19**] .
- Lutetium oxy orthosilicate (LSO) or lutetium yttrium oxyorthosilicate (LYSO) are the scintillator materials most widely used today in PET detectors due to their convenient physical properties for the detection of 511 keV annihilation photons. Natural lutetium contains 2.6% of ^{176}Lu which decays beta to excited states of ^{176}Hf. **[20]**
- ^{177}Lutetium (^{177}Lu) has the therapeutic radionuclide of choice due to its good physical properties. The emission characteristics of a therapeutic radionuclide should match the lesion size/volume to be treated to ideally focus energy within the tumour rather than in the tissue surrounding the lesion. **[21]**
- ^{177}Lu is a medium.energy β.emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration is less than 2 mm. ^{177}Lu is a reactor produced

radiometal that emits low.energy γ.rays at 208(10%) and 113 keV (6%) [**22**]

- 177Lu-EDTMP,177Lu-(Herceptin, Trastuzumab)177Lu-DOTATATE and Lu177-PSMA for theranostic applications in metastatic bone pain palliation, HER2 expressing Breast cancer, peptide receptor radionuclide therapy (PRRT) and Ca prostate therapy [**23**]

Decay characteristics of Rare earth radio isotopes

RADIOISOTOPE	HALF LIFE (T1/2)	BETA ENERGY	GAMMA ENERGY	AVAILABILITY
44Sc	4.0Hr	632Kev	1157Kev	Ti44-44Sc 44Ca (p,n) 44Sc
47Sc	3.35d	162kev	159 Kev (68%)	Research project
Y-90	64.1Hr	2.27Mev	Nil	Cyclotron, Generator
Ce141	32.5 days	434.6 (70.5%) 580(29.5%)	145.4(48.5 %)	Ce140(n, γ) reaction
142Pr	19.12Hr	2.162MeV (96.3%)	1575 KeV (3.7%)	141Pr (n, γ)
Nd147	10.98 days	233keV	91keV (28%) 531(13%)	Nd146(n, γ)
Pm147	2.62 years	62keV	121(0.002 %)	Nd147
Pm149	2.21 days	1.07meV	286(3%)	
Sm153	46.3Hr	640(30%) 710(50%),810(20%)	103(28%)	152Sm ((n, γ)
Eu152	4943 days		121(26%), 344(28%), 1408keV (20%)	Eu151(n, γ)
Gd153	240.4 days	41keV (60.5%) 104keV (29.5%)	nil	Gd 152(n, γ) Eu153(d,2n)
149Tb	4.12hr	730Kev (7.1%)	165(26.4 %)	EC
152Tb	17.5Hr	1.1Mev (20.3%)	271.1(9.5 %),344.3(63.5%)	EC, B+
155Tb	5.32 days		105.3(25.1 %),180.1(7.5%),262 .3(5.3%)	EC (100%)
161Tb	6.89 days	154Kev (100%)	25.6(23.2 %),74.6(1 0.2%),48. 9(17.0%)	B-, Auger effect
165Dy	140Min	1.3 MeV	108(3.8%)	164Dy (n,)
Ho166	26.8Hr	1.85Mev (48.8%),1.77 Mev (49.9%)	81KeV (6.6%)	Ho165(n,)
Tm170	128.4 days	968KeV (100%)	84KeV (3.26%)	Tm170(n,)
Lu177	6.7days	490keV (78.6%)	208KeV (11%) 113keV (8%)	Lu176(n,) Yb176(n,) Yb177-Lu177
Yb177	1.9Hr	1.4Mev (100%)	0.1089 Mev,1.2889 Mev	Yb176(n,) Yb177-Lu177

CONCLUSION:

The use of rare earth elements in medical applications is now well established. However, the future of diagnostic imaging analysis and therapy in Nuclear medicine may be heavily reliant on these paramagnetic elements. Rare earth elements demand is expected to soon outstrip supply. It also considers the possibility of reclaiming and reusing used or worn-out rare-earth elements, highlighting some companies that have begun to recycle the elements, including those derived from medical use, thereby reducing the demand for newly mined elements. Many new innovative ideas await us in the future.

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