Cumhuriyet Üniversitesi Fen Fakültesi
Fen Bilimleri Dergisi (CFD), Cilt:36, No: 3 Özel Sayı (2015)
ISSN: 1300-1949

Cumhuriyet University Faculty of Science
Science Journal (CSJ), Vol. 36, No: 3 Special Issue (2015)
ISSN: 1300-1949

Therapeutic Radiopharmaceuticals with Alpha Emitters, Properties and Microdosimetry

Seyed Mohsen SALEH KOOTAHI[1], Mohamad Javad SHAFEIE[*,2]

[1]*Assistant of Professor in Nuclear Department of K.N.Toosi university of Technology*

[2]*MSc of Nuclear Physics in Nuclear Department of K.N.Toosi university of Technology*

Received: 01.02.2015; Accepted: 05.05.2015

Abstract. Having useful properties in therapeutic radiopharmaceuticals, Radionuclides with alpha emitters plays a significant role in curing cancers. Some properties like short range and deposited energy in unit length of pathway cause to enhance the effect of alpha particle on destroying the DNA of cancer cells. Therefore, recognizing this capacity involves more investigations over the biological effect of these particles on human body. Properties of alpha emitters led to exert profound differences between this field and other fields of nuclear medicine. In order to understand the effect of alpha particles and optimizing the trend of corresponding research, Microdosimetry is considered as an influential tool.

Keywords: Alpha emitters, Radioimmunotherapy, Microdosimetry.

1. INTRODUCTION

Using alpha emitter radionuclide is a new way to cure cancers. The merits of alpha particles in curing cancers led to change the attention of users of beta particles towards alpha particles. In therapeutic radiopharmaceutical, attaching a radionuclide to the target tumor agent by nanostructure, antibodies, peptides, and small size molecule or natural mechanisms existing in the cancerous cell has been investigated by many researchers around the world, and this mechanism has been called as targeted therapy [1].

Targeted Alpha Therapy (TAT) is a method in which an alpha emitter radionuclide irradiates certain amount of radiation dose to tumor cells at early of event or during occurring metastasis and consequently destroys cancer cells. In contrast to other therapy methods like chemotherapy, this method paves the way for discriminating between the healthy cells and cancer cells, thereby reducing side effects of curing by these methods. In this study, we take a glance at the general properties of alpha emitters, dosimetry, and related affairs.

2. GENERAL PROPERTIES OF ALPHA RADIATION

Due to their short range and high LET (deposit energy in unit length of their pathway), Alpha particles have interestingly been taken into researchers' account. High LET inflicts irreversible damage to DNA in form of double stranded. To sterilize cancerous cells, almost 10 to 50 particle pathways are sufficient whereas in low LET particles like photon or Beta particles, it is in need of 1000 pathways [2]. Figure 1 compares alpha and beta particles LET in water The Absorbed dose of alpha particles is five times bigger than that of beta particles and external radiations resulted in giving rise to relative biological effectiveness (RBE).

*Corresponding author. *Email address: mshafeie@mail.kntu.ac.ir*

Special Issue: The Second National Conference on Applied Research in Science and Technology

http://dergi.cumhuriyet.edu.tr/cumuscij

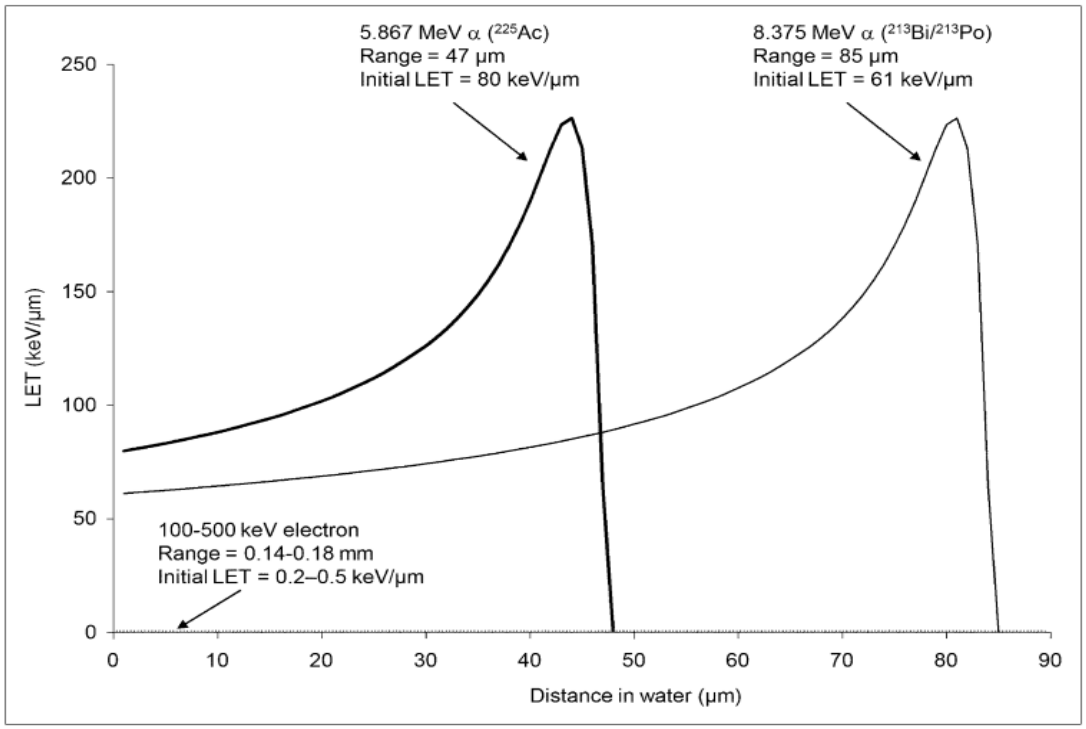

Figure 1. LET of Alpha and beta particles in water.

3. RADIOIMMUNOTHERAPY

To detect cancerous cells, applying natural mechanism of body immune system is one of the most important methods in cancer therapy. In this method, an alpha or beta emitter radionuclide attaches to a monoclonal antibody (AMB), possessing ability to detect antigen related to tumor, called alpha-immunoconjugate (AIC) [3]. In selecting an appropriate radionuclide for radioimmunotherapy, some issues like its proper half-life and availability should be taken into account. First of all, the decay mode of alpha emitter radionuclide receives a great attention. The stability of daughter nuclides and reaching nuclides on the stable status are of ideal conditions that are unattainable. One of the best alpha emitters for radioimmunotherapy is Astatine-211 with half-life of 7.2 h getting the stable state of Pb-207 by emitting alpha toward Bismuth and then capturing electron during 42 percent of undergoing time. Astatine-211 also goes to stable state of Pb-207 by capturing electron decays to polonium-211 and then emitting an alpha particle during 58 percent of decay time [4].

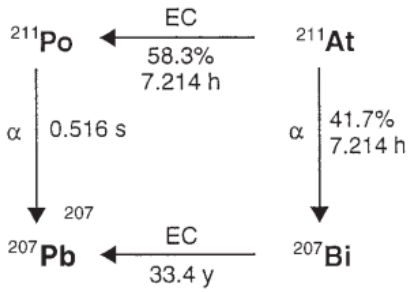

Figure 2. Decay mode of At-211.

The amount of energy of Alpha particle, suitable for radioimmunotherapy, produced by decaying At-211 is 5.87 MeV and 7.45 MeV, respectively. The LET of Astatine's alpha particles approximately is 100 KeV per micrometer which is in proximity with that of optimum RBE possessing high levels of lethal events. Po-211 has an x-ray with energy as much as 77-99 keV satisfying imaging and dosimetry purposes. Comparing to the other common therapy methods like chemotherapy, this method retaining x-ray radiations as a promising tool for studying the kinetics of radiopharmaceutical in human body, it consequently has been directed attentions to itself. Table 1 shows some properties of proper radionuclide for radioimmunotherapy.

Table 1. Alpha emitters radionuclide proper for nuclear medicine.

Radionuclide	z	Half-life	Alpha Average Energy(MeV)	Maximum Energy (MeV)	Average Range (μm)	<LET> (keV/μm)
^{211}At	85	7.2 h	6.79	7.45	60	71
^{213}Bi	83	45.6 min	8.32	8.38	84	61
^{223}Ra	88	11.43 d	5.64	7.59	45	81
^{225}Ac	89	10.0 d	6.83	8.39	61	71

In radioimmunotherapy, delivering AIC to the area of tumor is considered as a controversial issue. Due to some issues like heterogeneity of antigens and blood vessel, tumor received about 0.01-0.1 percent of injected labeled antibody. In this regard, some technics like pre-targeted therapy have been developed so as to tackle these problems [5].

4. MICRODOSIMETRY OF ALPHA EMITTERS

Radiation dosimetry is an efficient tool for studying radiation properties and also its effects on human tissue considered as a suitable tool for comparing different therapy methodologies. In a certain situation, traditional method of dosimetry as used for external radiation sources faces some important problems for alpha emitters. Concepts like average absorbed dose cannot be considered as a proper quantity for radiations with high LET. Moreover, the number of alpha particles crossing cell is low and therefore stochastic fluctuation becomes very important.

The particles crossing entire cell also consume a large amount of their energy, on the contrary, the ones scratching the surface of cells use low level or even zero level of their energy. Therefore, it is necessary to consider the nature of energy deposition in small target. With respect to consume a high level of alpha particles' energy in the short distance, some cells may collide with alpha particles and some do not. Since the range of Alpha particles is comparable to cell and subcellular structures, understanding the biological effect of alpha radiation on single cell is received great attention [6].

The basic quantity in Microdosimetry is special energy (**z)** which defined as energy deposit (in Joule) per target mass (in kilogram). This quantity has same unit as absorbed dose, Gray (Gy), but the difference between them lies in stochastic nature of alpha radiation which is neglected in ordinary dosimetry.

$$z = \frac{\varepsilon}{m} \tag{1}$$

This quantity uses to estimate survival fraction (SF):

$$SF = e^{-\frac{z}{z_0}} \tag{2}$$

z_0 is absorbed dose needed to cell survival fraction become 37 percent.

There are three general approaches being available for Microdosimetry: High resolution solid state micro dosimeter, analytical codes, and Mont Carlo simulation codes. In terms of calculation affairs, Analytical codes, by enjoying Fourier transform, are very efficient, but they are limited to the simple geometry because single event-spectrum should be known for every source-target configuration. Mont Carlo codes have more flexible for more complicated configuration. In all of these approaches, deposited energy of single particle spectrum obtained and then by analyzing this spectrum, different kinds of data will be achievable [7].Researches show stochastic fluctuations in deposited energy should be taken in account when relative deviation from local dose is higher than 20 percent. As Microdosimetry approaches mainly depend on source distribution, size and shape of target and expected average dose, the importance of Microdosimetry will be highlighted in the medium and small doses (i.e. non-targeted tissues) whereas in tumor with possible bigger average dose, this idea is not effective. [8].

5. EFFECT OF DOSE RATE AND DOSE FRACTION

The effects of dose rate on low LET radiation have been substantiated. If the rate of dose rate is decreased and conversely time of irradiation is increased, the biological effects will generally be decreased due to providing enough time to repair the undermined DNA. As Damages inflicted by high LET radiations are almost irreparable, the dose rate must not influence on cell survival. According to the results of related studies, a clear effect of alpha particles at 0.5 -100 rad/min on cells has not been observed.

In external radiation therapy, owing to the capacity of trivial repairing in healthy tissues in comparing to cancerous tissues, the radiation dose is delivered to cancerous cells in several times. It is necessary to say that this condition on alpha particle's radiation is not applicable because of the high level of ELT energy in alpha particles. This means that the effect of delivering a determined dose of radiation equals to delivering the total dose of radiation in the same fragments to patients [9].

6. CLINICAL TRIALS

Designing clinical trials requires gaining complete knowledge about all physical and biological factors influencing on the reactions of tumor and healthy tissue. In this regard, dosimetry plays a significant role in directing clinical trials. Although, Alpha therapy possesses high percentage of effectiveness, it can also cause to poison the healthy tissues. Collecting a wide range of information about bio-distribution of radiopharmaceutical in body through animal trials or in vitro trials and then dosimetry calculation (by simulation codes like Geant 4) can assist to design more proper clinical trials. Moreover, the effects of all kinds of possible phenomena such as secondary electrons and Auger electrons produced by ionization radiation and also behavior of daughter nuclei and their biological distribution are crucial to estimate the level of deterministic and stochastic risk.

7. CONCLUSION

These days, alpha emitter radiopharmaceuticals are going to be an important part of cancer therapy in nuclear medicine. Designing alpha agents has been considered as a controversial

issues, thereby requiring appropriate theoretical and practical tools to be improved (i.e. more accurate simulation codes).

REFERENCES

[1] George Sgouros, PhD, and Robert F. Hobbs, PhD (2014) Dosimetry for Radiopharmaceutical Therapy Semin Nucl Med 44:172-178 C 2014 Elsevier Inc

[2] George Sgouros (2008) Alpha-particles for targeted therapy,Advanced Drug Delivery Reviews 60 (2008) © 2008 Elsevier B.V

[3] Mauro Valente,Francisco Malano,Pedro Pérez(2013) Internal dosimetry for alpha emitters radiopharmaceuticals in biological tissue studied with the FLUKA code, Latin American Symposium on Nuclear Physics and Applications (X LASNPA), December 2013 Montevideo, Uruguay

[4] Olivier Couturi er, Ste´phane Supiot et.al.(2005),Cancer radioimmunotherapy with alpha-emitting nuclides European Journal of Nuclear Medicine and Molecular Imaging Vol. 32, No. 5, May 2005

[5] Richard J. Kowalsky Steven W. Falen, (2004) Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, by the Ame rican Ph armacists Ass ociation. 2004

[6] Chen-Yu Huang, Susanna Guatelli, Bradley M. Oborn, and Barry J. Allen (2012),Microdosimetry for Targeted Alpha Therapy of Cancer, Hindawi Publishing Corporation, Computational and Mathematical Methods in Medicine,Volume 2012, Article ID 153212,July 2012

[7] Ruby Meredith, MD, PhD, Barry Wessels, PhD, and Susan Knox, MD, PhD,(2008) Risks to Normal Tissues From Radionuclide Therapy, Semin Nucl Med 38:347-357 © 2008 Elsevier Inc.

[8] Patei Riddhi D, Dr. P.M.Patel , Dr. N.M.Patel (2011) A Review on Radiopharmaceuticals and Radiochemical Method in Analysis, International Journal of Pharmaceutical & Biological Archives 2011

[9] George Sgouros, John C. Roeske et.al (2010),MIRD Pamphlet No. 22 (Abridged):Radiobiology and Dosimetry of alpha-Particle Emitters for Targeted Radionuclide Therapy, THE JOURNAL OF NUCLEAR MEDICINE • Vol. 51 • No. 2 • February 2010