Nuclear Medicine Therapy

-Radioisotopes Production and Dosimetry-

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ΠΕΡΙΕΧΟΜΕΝΑ

ΕΙΣΑΓΩΓΗ

Η πυρηνική ιατρική παρέχει αποτελεσματικά εργαλεία για τη θεραπεία του καρκίνου χρησιμοποιώντας ραδιοφάρμακα τα οποία εκπέμπουν α-, β- σωματιδιακή ακτινοβολία ή ηλεκτρόνια Auger.

Λόγω της μικρής ελεύθερης διαδρομής, αυτά τα σωματίδια έχουν την ικανότητα να καταστρέφουν κυρίως καρκινικά κύτταρα με ταυτόχρονα ελάχιστη ακτινική επιβάρυνση των πέριξ ιστών.

Η ιδανική εφαρμογή για στοχευμένη θεραπεία με ραδιοφάρμακα απαιτεί την εξαιρετική γνώση των φυσικών, βιολογικών και χημικών ιδιοτήτων αυτών των ραδιονουκλεϊδίων. Για τη βελτίωση του θεραπευτικού αποτελέσματος, είναι απαραίτητο να γίνεται εξατομικευμένη δοσιμετρία κάθε ασθενούς, στα υγιή και στα καρκινικά όργανα.

Γίνεται επισκόπηση των ραδιοφαρμάκων που χρησιμοποιούνται στη θεραπεία, περιλαμβάνοντας τον τρόπο παραγωγής τους, την βιοκινητική και τη δοσιμετρία τους.

Τα πλέον σημαντικά κριτήρια στην επιλογή ενός ραδιονουκλεϊδίου για θεραπευτική χρήση είναι τα κατάλληλα φυσικά χαρακτηριστικά του και η βιοχημική του αντίδραση. Ο επιθυμητός χρόνος ημιζωής είναι μεταξύ μερικών ωρών και ολίγων ημερών. Η εκπεμπόμενη σωματιδιακή ακτινοβολία πρέπει να έχει κατάλληλο εύρος γραμμικής μεταφοράς ενέργειας (LET) στον ιστό. Υψηλή ραδιοχημική καθαρότητα και υψηλή ειδική ραδιενέργεια είναι, επίσης, απαραίτητες ιδιότητες των θεραπευτικών ραδιονουκλεϊδίων. Στην περίπτωση που εκπέμπεται και διεισδυτική γ- ακτινοβολία, ο λόγος της μη διεισδυτικής σωματιδιακής προς την διεισδυτική γ- πρέπει να είναι υψηλός. Το θυγατρικό νουκλεΐδιο που παράγεται πρέπει να είναι βραχύβιο ή σταθερό.

Η βάση για επιτυχημένη θεραπεία με ραδιοϊσότοπα περιλαμβάνει και την εκλεκτική και επαρκή συγκέντρωση καθώς και την παρατεταμένη παραμονή του ραδιοφαρμάκου στον όγκο, ενώ η πρόσληψη από τους υγιείς ιστούς πρέπει να είναι ελαχίστη.

Η παραγωγή των ραδιονουκλεϊδίων για θεραπεία γίνεται σε πυρηνικούς αντιδραστήρες ή κατά τον βομβαρδισμό φορτισμένων σωματιδίων σε κυκλοτρόνια και επιταχυντές. Συστήματα γεννητριών έχουν επίσης αναπτυχθεί και προσφέρουν πρακτική λύση, όπως $^{90}Sr->^{90}Y$ και $^{188}W->^{188}Re$ σε περιπτώσεις χρήσης βραχύβιων ραδιοϊσοτόπων στην θεραπεία με ραδιοφάρμακα.

Για να επιτευχθεί το αποτέλεσμα της θεραπείας με ραδιοφάρμακα, είναι σημαντική η συσχέτιση της απορροφουμένης δόσης στον ιστό ως αποτέλεσμα της ακτινοβολίας που εκπέμπει το ραδιονουκλεΐδιο και του βιολογικού αποτελέσματος. Επομένως, είναι ουσιαστική η γνώση της δοσιμετρικής μεθοδολογίας και η εκτίμηση του αποτελέσματος της θεραπείας σε σχέση με την χορηγούμενη ακτινοβολία. Για την επίτευξη του βέλτιστου αποτελέσματος της θεραπείας ανά ασθενή, εφαρμόζεται η εξατομικευμένη δοσιμετρία με την χρήση παραμέτρων και βιοκινητικής του ραδιοφαρμάκου.

Σήμερα, λογισμικά που παράγουν μοντέλα όγκων 3-διαστάσεων δίδουν την συσχέτιση της συνολικά εναποτεθειμένης δόσης στον όγκο και αναδεικνύεται η πιθανά ανομοιογενής κατανομή του ραδιοφαρμάκου στα κύτταρα αυτού που οδηγεί σε μη ομοιόμορφη απορροφουμένη δόση στο εσωτερικό του όγκου.

Abstract

Nuclear Medicine provides efficient tools for cancer therapy using compounds labelled with radionuclides that emit beta-particles, alpha-particles or Auger electrons. With their short path lengths, they destroy mainly targeted cancer cells with limited side effects. Ideal application for targeted radionuclide therapy demands radionuclides' physical, radiobiological and radiochemical properties to be well known. These radionuclides are produced with the desirable characteristics for their application in Nuclear Medicine radiopharmaceutical therapy.

Furthermore, measurements of absorbed dose to the abnormal and to the normal tissue, in a patient-specific point of view, enhance therapy effectiveness. Dosimetry is a valuable tool for the decision of a successful treatment that will give impressive anti-tumour results and favourable tumour-to-normal tissue ratios.

This article will be a review of the contributions both in the production of the radionuclides – dedicated to radiopharmaceutical therapy – as well as in the individualized dosimetric methods referred in the literature for each radionuclide used in Nuclear Medicine therapy. Many dose-calculation methods and mathematical codes used will be referred in detail.

Keywords: Radionuclides, Production, Physical Characteristics, Dosimetry, Biokinetic Properties

I) INTRODUCTION

i) Therapeutic Radionuclides

The challenges inherent in the development of radionuclide therapy arise from the need to strike a perfect balance between specific accumulation into target and a quick clearance of the radioactivity from non-target sites. The design and development of such agents have undergone from small organic molecules or inorganic moieties that were used, to present-day research that make use of antibodies, peptides, steroids, nucleotides and other small molecules that have specific receptor affinity.

Among the radionuclides used for cancer therapy, ^{131}I, ^{90}Y, ^{188}Re, ^{166}Ho or ^{153}Sm are applied for the treatment of a multitude of malignant disorders; they have been used for cancer therapy, palliation of bone pain arising from secondary metastases, radio-synovectomy or intravascular radiation therapy. Extensive research in the field of radiopharmaceutical practices have led to the identification of other radionuclides, including ^{177}Lu, ^{67}Cu or alpha emitters such as ^{211}At, with promising physical and chemical properties [1].

ii) Therapeutic Radionuclide Choice Criteria

The major criteria for the choice of a radionuclide for therapeutic use are suitable decay characteristics and biochemical reactivity. Regarding the decay properties, the desired half-life is between few hours and several days; the emitted particles of radiation should have an appropriate linear energy transfer (LET) value and range in the tissue; high radionuclide purity, high radiochemical purity and high specific radioactivity are necessary properties, as well.

The three types of therapeutic radionuclides are β-emitters, α-emitters and Auger electron emitters. The ratio of non-penetrating to penetrating radiation should be high. The daughter nuclide should be short-lived or stable [2]. The basis for successful radionuclide therapy incorporates selective and sufficient concentration as well as prolonged retention of the radiopharmaceutical in the tumour while the uptake in normal tissue should be kept at the lowest levels.

iii) The Ranges of Emitted Particle Radiation in the Tissue

In radiopharmaceutical therapy, the β-particles have ranges from 1 mm depending upon their energies. They can lead to therapy effects even if they reach the cell environment and the therapeutic applications have been more straightforward, though not very specific. The α-particles have a range of about 100 μm and can have a therapy effect only if they reach the cell membrane, e.g. by attachment of the α-emitter to a receptor ligand. The Auger electrons have a range of about 10 μm and can have a therapy effect only if they reach the cell nucleus,

e.g. by bringing the radioactive source atom to the DNA. The effect of low-energy-high-intensity electrons, emitted following e-capture (EC) and isomeric transition (IT) is not negligible and therefore all sources of secondary electrons must be taken into account [3].

iv) Production Data

The production of radionuclides for use in therapeutic treatments is achieved through nuclear reactions in reactors or from charged particle bombardment in cyclotrons and accelerators. The number of β-emitters of therapeutic relevance is relatively large. Most of the β-emitters are produced in a nuclear reactor, and data are needed on neutron capture and fission yields. In a nuclear reactor, the (n,γ) process is commonly utilized for production purposes. The major interest is in the low energy region. The specific radioactivity achieved is rather low unless the activated product decays to a daughter radionuclide which could be chemically separated and used in medical applications. With a view to enhancing the specific radioactivity, the β^- decay daughter of an (n,γ)-product is used, *e.g.* ^{110}Pd $(n,\gamma)^{111m}$Pd$\rightarrow^{111}$Ag. The isotopic abundance of the target isotope and the neutron flux in the reactor is limited by the cross section of the (n,γ) reaction [4, 5].

An alternative route of production involves the use of an (n, p) reaction in a fast neutron field. The (n, p) reaction is utilized to produce therapeutic radionuclides in the medium and heavy mass regions, besides its use in the light mass region. High-intensity machines are capable of providing such fast neutron fields and the production e.g. of ^{67}Cu and ^{89}Sr via the respective (n, p) reaction appears very advantageous [6]. Another important production process is the fission of ^{235}U which gives rise to ''no-carrier-added'' products.

Cyclotron and accelerators produced isotopes are, nowadays, finding extensive therapeutic applications. This production is described through interaction of charged particles, such as protons, deuterons and alphas, with matter. An example of the cyclotron produced isotopes, used for treatment, is the production of alpha particle emitting isotopes, as ^{211}At and ^{213}Bi, for targeted therapy of lesions [7].

Generator systems are, also, developed and offer a solution, *e.g.* ^{90}Sr$\rightarrow^{90}$Y and ^{188}W$\rightarrow^{188}$Re, in use of short lived radioisotopes sources for radiopharmaceutical therapy.

v) Nuclear Data – Production Cross-Section – Production Yield

The improved quality of the nuclear data will make reactor and accelerator production of therapeutic radionuclides much more efficient and effective; quality enhancement is also obtained through improved purity. In order to provide standardized data for the production of relevant radioisotopes, IAEA in "Nuclear Data for the Production of Therapeutic Radionuclides" [8] proposes recommendations for both established and emerging radionuclides.

The terms cross-section and yield, widely used in practical radioisotope production, often differ from basic definitions; cross-section, in radionuclide therapy, means elemental production or isotopic production cross-section of the final nuclide. When an accelerated charged particle interacts with a target nucleus, a nuclear reaction takes place. In isotope production, usually, the activity of the product radioisotope is measured. The related quantity of interest is, then, the production cross-section. It refers to a sum of cross-sections of all reaction channels on a well-defined target nucleus, which lead to direct production of the final nuclide. The same final nuclide can also be produced indirectly via the decay of progenitors produced simultaneously on the target nucleus.

The yield for a target having any thickness can be defined as the ratio of the number of nuclei formed in the nuclear reaction to the number of particles incident on the target. It is termed as the physical yield. It is customary to express the number of radioactive nuclei in terms of the activity and the number of incident particles in terms of the charge. Thus, yield, Y, can be given as activity per Coulomb, in units of GBq/C. When the irradiation time is much longer than the half-life of the produced isotope, a saturation of the number of the radioactive nuclei present in the target is reached and the activity produced by a unit number of incident beam particles is the saturation yield [9].

vi) Dosimetry in Therapy by Radiopharmaceuticals

To achieve the treatment objective in radionuclide therapy, it is important to relate the dose absorbed in the tissue as an effect of energy absorption and the response results dominated by biological factors [10]. It is essential, therefore, to understand the dosimetry methodology and evaluate the radiopharmaceutical therapy effects relative to the radiation induced. The accuracy in dosimetry depends on the accuracy of the available decay and biochemical data. The biological effects of radionuclide therapy are mediated via a well-defined physical quantity, the absorbed dose, which is defined as the energy absorbed per unit mass of tissue. In the case of therapeutic radionuclides, the absorbed dose has to be high enough to achieve the therapeutic effect.

The basic formulation and subsequent practical methodologies for estimating absorbed dose was established by the MIRD Committee which first published a table of S values, making possible the conversion of cumulated activity in different organs to absorbed dose. A fixed geometry model was adopted to calculate the S values. S values derived from fixed geometry models have the advantage of not requiring point-kernel or Monte Carlo calculations in estimating absorbed dose [11].

Average organ doses can be estimated using MIRDOSE3 with appropriate corrections for patient's organ mass, whole body mass, activity administered and other individualized data [11]. A novel feature for future computations of dose is the ability to separate organs. The

requirements of therapeutic nuclear medicine have led to such ongoing refinements in the fixed geometry models used to derive S values so as several organ-specific and whole-body age-specific models have been developed and are included in OLINDA, a software package that implements the fixed model approach to absorbed dose calculation [12, 13]. Using this package, the absorbed dose of each organ and the effective dose of the radiopharmaceutical can be calculated [10]. Other phantoms for dosimetric calculations are the voxel phantoms family, human models based on computed tomographic or magnetic resonance images obtained from high-resolution scans. They consist of a huge number of volume elements (voxels) and offer a clear improvement over the MIRD-type mathematical phantoms. Voxel phantoms can be applied also in radionuclide therapy; however, for patient specific absorbed doses, a phantom for every individual patient is necessary. This will be possible when the segmentation procedures have improved and the creation of a phantom is quick so as to be completed in a couple of hours [14]. Fixed geometry models have the disadvantage, however, of not matching the actual patient anatomy [14]. This disadvantage is being addressed by developments in 3D imaging-based patient specific dosimetry software.

vii) Importance of Patient Specific Dosimetry

One of the limiting factors in utilizing therapeutic radiopharmaceuticals is the potential hazard to the bone marrow, kidneys and other internal organs. The smaller peptide molecules, used nowadays, may get out of the system rapidly but still cause damage as they pass through the various organs [15]. The tolerable limits vary from patient to patient depending on the volume of the kidneys and other critical organs, the rate of excretion and other varying individual factors [16]. Therefore, it is important to determine the therapeutically effective dose for each patient specifically.

The established method for individualized dosimetry is based on the measurement of the biokinetics by series of planar gamma camera images followed by calculations of the administered activity and the residence times, resulting in the radiation-absorbed doses of critical organs [17, 18]. The quantification of the activity from planar data in different organs is inaccurate due to the lack of attenuation and scatter corrections and background organ overlay. Dosimetry based on quantitative 3D data is more accurate and allows a patient specific approach. Inhomogeneous accumulation of the radionuclide in an organ can be detected, as well. Many efforts to improve the spatial distribution of absorbed dose to specific patient anatomy have lead to the development of relative software [19].

Evidence of renal toxicity has highlighted the need to examine additional dosimetric parameters such as the dose rate and the spatial distribution. The rate of absorbed dose delivery has been, up to date, largely ignored. There is also some evidence in radionuclide therapy that absorbed dose rate should not be neglected in trying to predict response [20]. The

importance of dose rate will increase as lower molecular weight agents gain widespread use; these agents clear rapidly and require greater administered activities. Nowadays, software generating a 3D solid tumour model has been created. Modified Monte Carlo codes have been used for simulation therapy with beta emitters applied on the tumour cells [19, 21]. Moreover, heterogeneity of intra tumoural distribution of administered radionuclides leads to non-uniform absorbed dose.

An accumulated dose volume histogram (DVH) showed that most tumour cells received a lower dose than average tumour absorbed dose. This discrepancy between conventional and cellular approach show that dosimetry on cellular level is necessary for a better selection of radionuclide and optimal calculation of administered activity in the radionuclide therapy. For small tumours and micro-metastases, the electron energy which escapes the tumour volume cannot be neglected and must be calculated for the specific radionuclide, tumour mass and shape. The absorbed fractions in tumours with small radii are greater with low energy beta emitters [21].

One possible approach would be DVHs representing dose distributions in targeted radionuclide therapy. Monte Carlo simulations can give differential and accumulated DVH as the best method for the presentation of the cell dosimetry in the radionuclide therapy. The basic concept of treatment in the radionuclide therapy must be a generation of optimal DVHs for an individual therapy plan [21]. With an absorbed dose calculation at the cellular level it is possible to achieve this goal and improve radionuclide therapy effects. DVH could put the radionuclide therapy plan on the same methodological level as the external radiotherapy.

Further in this text we provide adequate information on therapy using various radiopharmaceuticals – α-particles, β-particles and Auger electron emitters – as a review of the contributions both in the production of their radionuclides and in the dosimetric methods referred in the literature for each radionuclide used. Going through dose-response studies from different institutions, absorbed dose methodology will be unfolded.

II) RADIOISOTOPES

i) Phosphorus-32

Introduction

Phosphorus-32 (^{32}P) was the first radionuclide introduced more than 50 years ago for the palliation of pain from bone metastases. From the 1940s to 1980s it was the most widely used radionuclide. ^{32}P has also been used in therapy of polycythemia vera and leukemia.

Production and Physical Characteristics

^{32}P was one of the first radioactive isotopes to be prepared in cyclotron for therapeutic research purpose. It was produced in the Berkley cyclotron by E. Lawrence in 1936 [22]. ^{32}P was produced by irradiating red phosphorus ($^{15}P_{31}$) with deuteron ($^{1}H_{2}$) according to the reaction [23]: $^{15}P_{31}+^{1}H_{2}\rightarrow^{15}P_{32}+^{1}H_{1}$. The cross section of the reaction is about $0.18*10^{-27}$ cm^2. Nowadays, with the development of nuclear reactors, radiophosphorus is produced primarily from bombarding sulfur ($^{16}S_{32}$) with fast neutrons: $^{16}S_{32}+n\rightarrow^{15}P_{32}+^{1}H_{1}$. The product is practically carrier-free. ^{32}P has a physical life of 14.3 days. It emits a β-particle with a maximum energy of 1.71 MeV and an average mean energy of 0.70 MeV. The mean and the maximum particle range in soft tissue are 3 and 8 mm, respectively.

Uptake and Biokinetic Properties

^{32}P has been used in a variety of chemical forms such as sodium orthophosphate (Na_2HPO_4), polymetaphosphate ($Na_6O_{18}P_6$), pyrophosphate (P_2O_7) and hydroxyethylidene diphosphonate (HEDP). Tofe *at al*. [23] reported that ^{32}P-HEDP was approximately 20 times more concentrated in the bone mineral than ^{32}P. Commonly it is used as orthophosphate. The radiopharmaceutical is administrated by intravenous injection or orally. A typical administrated activity is about 444 MBq (12 mCi) fractionated.

Its uptake depends on several factors such as the total exchangeable phosphate in the tissue, the metabolic activity of the tissue and the nature of phosphorus labeling. 85% of total body phosphate is deposited in the skeleton and about 15% in muscle, liver and spleen [24]. Approximately 5-10% of the administrated activity is excreted via urine and faeces within 24 hours and about 20% within 1 week.

Erf and Lawrence [25] studied the distribution of radiophosphorus and excretion in normal individuals and patients with leukemia. It was detected that leukemic tissues retained more radioactive phosphorus than normal tissues. A second important observation showed that when ^{32}P was administrated orally the same percentage (15 to 50%) of ^{32}P was excreted in the urine and feaces, in both normal individuals and patients. When ^{32}P was administrated intravenously the excretion in patients was significantly less (5 to 25%). In addition, it was found that in leukemic patients more phosphorus was retained when the administration was intravenously than orally. Reinhard *et al*. [24] reported that patients with diseases of tissues (leukemia, polycythemia) and osseous metastases showed diminished phosphorus excretion. The tumour to normal bone ratio for ^{32}P was found approximately 2:1 [26]. In 1950, Hertz [27] observed that androgens increased the uptake of phosphorus. This observation led to the combined use of androgens or testosterone and radioactive phosphorus. According to Maxfield [28], pretreatment with testosterone gave a therapeutic ratio of 20:1 for tumour to normal bone. Kenney [29] estimated the absorption ratio of radioactive phosphorus in patients

with breast cancer, osteogenic sarcoma and lymphosarcoma. It was found that phosphorus was absorbed more by the tissue of osteogenic sarcoma and lymphosarcoma and less by breast cancer.

Dosimetry

Spiers *et al*. [30] reported on the determination of absorbed dose to bone marrow in the treatment of polycythaemia by ^{32}P. Total marrow absorbed dose was found to be 3.8 mGy/MBq (or 140 mGy/mCi) and the bone dose was estimated at 17 mGy/MBq (or 630 mGy/mCi). The whole-body biological life had a mean value of (39.2±4.5) days. Potsaid [31] treated 5 patients with bone metastases from prostate cancer with ^{32}P-HEDP. 2 patients received 333 MBq (9 mCi) and 3 patients received 111 MBq (3 mCi) intravenously. With an administrated dose of 3 mCi of ^{32}P-HEDP the total bone marrow absorbed dose was found 2.48 Gy (248 rads). The contribution from marrow itself, trabecular and cortical bone was 0.56, 1.85 and 0.07 Gy (56, 185 and 7 rads), respectively. According to ICRP report No 53 [32], the effective dose of ^{32}P for adults is given as 2.4 mSv/MBq with the absorbed dose to bone marrow as 11 mGy/MBq (407 mGy/mCi).

ii) Copper-67

Introduction

Due to its excellent physical and biochemical properties for radioinimunotherapy, Copper-67 (^{67}Cu) is being actively investigated by several groups as a radioimmunotherapeutic agent [33-37]. ^{67}Cu is referred as isotope of high priority and due to a 2.6 days half-life and suitable β-emission (141 keV, avg) is ideal for use with MAbs and other tumour targeting compounds. Cu-67 has a cross section value gradually increase, above 60 MeV-high energy reactions.

Production and Physical Characteristics

^{67}Cu is produced by the Zn-68 (p,2p) reaction, which also produces ^{64}Cu ($T_{1/2}$ = 12.7 h), ^{61}Cu ($T_{1/2}$ = 3.4 h), and other radionuclides. Radiometals other than the isotopes of copper are quantitatively removed [38]. Copper-61 decays rapidly to negligible activity, but ^{67}Cu remains present in appreciable quantities for days. The ratio of ^{67}Cu to ^{64}Cu to ^{61}Cu activity is typically 1:7:10 at end of bombardment, or 1:0.5:0.0001 when received by the customer (48-72) hrs later. To produce radiopharmaceutical of adequate amount and specific activity, ^{67}Cu-2IT-BAT-Lym-l is usually prepared for clinical use within 24 h of receipt of the radionuclide [38] at which time the activity of ^{64}Cu is still significant. A method to measure the activities

of ^{67}Cu and ^{64}Cu in a mixed sample is needed to dispense a correct dose of radiopharmaceutical.

^{67}Cu releases beta particles with mean energies and abundances of 121 keV (56%), 154 keV (23%) and 189 keV (20%) that are suitable for therapeutic purposes and photons with energies and abundances of 91 keV (7%), 93 keV (16%) and 184 keV (49%) that are suitable for imaging purposes.

^{67}Cu contains ^{64}Cu radioimpurity as a co-product. Because the half-life of ^{64}Cu (12.7 h) is much shorter than that of ^{67}Cu (61.9 h), the ratio of ^{64}Cu to ^{67}Cu decreases after the end of bombardment (EOB). The average amount of ^{64}Cu as a percent of total activity in the supply at the time of delivery, typically 36-48 h after EOB, is 43% (range (35-61)%). In addition to photons (1346 keV (0.5%)), ^{64}Cu emits positrons that generate annihilation photons (511 keV (36%)). These high-energy photons readily penetrate the septum of a gamma-camera collimator and can thus alter quantization of the intended ^{67}Cu radiopharmaceutical. ^{64}Cu also affects radiation dosimetry.

Uptake and Biokinetic Properties

^{67}Cu is readily transferred from the usual chelates or EDTA or DTPA to albumen. Bifunctional chelating agent p-bromoacetamidobenzyl-TET was conjugated into Lym-1, a monoclonal antibody against human B cell lymphoma, without significantly altering its immunoreactivity. This conjugate was stably labelled with ^{67}Cu under conditions chosen to optimize the yield of a high specific activity radiopharmaceutical. The biodistribution in RAJI tumour bearing mice demonstrated significant tumour uptake (14.7% ID per gram) and extended residence time (120 hr) in contrast to normal organs. After 24 h, radioactivity was continuously cleared from all tissues except the tumour [39].

Dosimetry

In many studies a line source and a small vial source of ^{67}Cu containing varying amounts of ^{64}Cu were used to evaluate the impact of ^{64}Cu on image resolution and activity quantization, respectively. Identical pharmacokinetics for ^{67}Cu and ^{64}Cu were assumed, and the radiation dosimetry of ^{64}Cu was assessed using quantitative imaging data as the amount of ^{64}Cu could be calculated any time after ^{64}Cu production. MIRD formalism was used to estimate the therapeutic index, defined as the ratio of radiation dose to tumour divided by the radiation dose to bone marrow.

In another study [40], pharmacokinetic data from 4 patients were evaluated for 12 doses of ^{67}Cu-2IT-BAT-Lym-l ranged from 0.48 to 5.25 GBq (13-142 mCi). The maximum amount of ^{64}Cu at injection time was 20%, while the average was 12%. Briefly, planar images of conjugate views were acquired immediately, 4 h and daily up to 10 days after administration

of [67]Cu-2IT-BAT-Lym-l. The amount of activity in organs and tumours was determined using geometric mean or effective point source methods, depending on whether the source object could be identified on both conjugate views.

In another analysis [41], it was assessed the ability of Copper-67 ([67]Cu)-C595 murine antimucin monoclonal antibody to bind selectively to superficial bladder tumours when administered intravesically, with a view to its development for therapy. Approximately 20 MBq of [67]Cu-C595 monoclonal antibody was administered intravesically to 16 patients with a clinical indication of superficial bladder cancer. After 1 hour, the bladder was drained and irrigated. Tissue uptake was assessed by imaging and by the assay of tumour and normal tissues obtained by endoscopic resection.

iii) Strondium-89

Introduction

Strontium-89 (^{89}Sr) is the most commonly used radionuclide in the treatment of metastatic bone cancer. It was first reported by Pecher in 1942 [42]. Firusian *et al*. [43] and several other researchers explored the utility of ^{89}Sr in the palliation of bone pain from osseous metastases. [89]Sr was the first radionuclide approved from US Food and Drug Administration (FDA) for its routine application in 1993.

Production and Physical Characteristics

[89]Sr is a pure beta emitter. It has a physical life of 50.5 days and maximum β-particle energy of 1.46 MeV. The maximum and the average range in soft tissue are approximately 6.7 mm and 2.4 mm, respectively. [89]Sr is typically used as chloride salt [89]$SrCl_2$.

At the present time, there are two major methods of ^{89}Sr production [44]. The first consists of irradiating a highly enriched target of [88]Sr ([88]Sr > 99.9%) with neutrons according to [88]Sr (n,γ)[89]Sr reaction. This is a simple production taking place in thermal neutron reactors. The second method, based on threshold reaction with emission of charged particles according to [89]Y (n, p) [89Sr] reaction, occurs in fast flux reactors. The small cross section of the reactions ($6*10^{-27}$ cm^2 and $0.3*10^{-27}$ cm^2 respectively) restricts the productivity of these two methods. Consequently there is a need for a more efficient method for the production of [89]Sr.

Recently, a new way for ^{89}Sr production with solution in a reactor was proposed [45]. Corresponding to this way, the gaseous radionuclide [89]Kr decays to [89]Sr: [89]Se→[89]Br→[89]Kr→[89]Rb→[89]Sr. In this case the cross section is almost 500 times greater than in neutron capture reaction. This new technology produces almost no radioactive waste with principal advantage of high ^{89}Sr productivity.

Uptake and Biokinetic Properties

^{89}Sr behaves biologically like calcium. After intravenous administration approximately 50% of ^{89}Sr is localized in bone, primarily in areas of osteoblastic metastases. Concerning the ^{89}Sr not concentrated in bone, about 80% is excreted through the kidneys and 20% through the gastrointestinal system.

Breen *et al*. [46] presented that Strontium retention correlates positively with the degree of osteoblastic metastatic bone involvement. The whole-body retention and plasma concentration were calculating according to the ICRP model [47]. The strontium concentration in metastatic areas was found to be 2 to 25 times greater than that in normal bone. The ^{89}Sr renal plasma clearance rate was ranged from 4.1 to 12.8 d^{-1}.

Blake *et al*. [48] treated 14 patients with osseous metastases due to prostate cancer. Three of the patients received 1.48 MBq/kg (60 μCi/kg) of body weight and the subsequent patients received 2.22 MBq/kg (60 μCi/kg) of ^{89}Sr with a tracer dose of ^{85}Sr. Plasma clearance curves were obtained and urine was collected. A whole body counter was used to monitor the Strontium retention. The total body retention was calculated by Marshall Model [47]. It was found that at 90 days, the retention of ^{89}Sr varied from 11% in patients with limited metastatic involvement to 88% in patients with extensive involvement. The Strontium renal plasma clearance was varied from 1.6 to 11.6 d^{-1}. In normal bone the biological half-life is approximately 14 days compared to more than 50 days in bone metastasis. In another report, Blake *et al*. [49] found that ^{89}Sr retention varies indirectly with renal plasma clearance rate – the higher degree of Strontium retention the lower plasma concentration. The ^{89}Sr renal plasma clearance was ranged from 0.1 to 11.8 d^{-1}.

Dosimetry

Blake *et al*. [50] reported on 2 patients with painful bone metastases from prostate cancer who both received therapeutic doses of ^{89}Sr of 2.22 MBq/kg (60 μCi/kg) of body weight. Simultaneously, the patients were injected with a tracer dose of about 37 MBq (1 mCi) of ^{85}Sr-chloride in order to image the kinetics of the ^{89}Sr with scintigraphy. Injection, with the same administrated dose, was repeated 6 months after the first treatment. The volume of the metastases was determined from high resolution computed tomography (CT) images and the bone density was calculated from the mean Hounsfield unit. The ICRP dosimetric model for bone (ICRP 30) [51] was used to estimate the mean absorbed dose to metastases utilizing additionally the scintigraphic measurements. The mean absorbed dose to metastases was found 20 cGy/MBq (740 cGy/mCi) and 24 cGy/MBq (889 cGy/mCi) for the two patients. To estimate the absorbed dose to red bone marrow, the kinetic model proposed by Reeve and Hesp [12] was added to the ICRP 30 model. The mean absorbed dose to red bone marrow was

calculated 2 cGy/MBq (74 cGy/mCi) suggesting a ratio of approximately 10:1 of tumour to bone marrow absorbed dose. Also, the patients showed different hematological response.

One year later, the same group [49] studied 10 patients with skeletal metastases. Patients received a therapeutic injection of ^{89}Sr of 1.48, 2.22 or 2.96 MBq/kg (40, 60 or 80 μCi/kg) of body weight together with a tracer dose of 37 MBq (1 mCi) of ^{85}Sr. Following the same method of dose estimation (imaging and ICRP model), the absorbed dose was found to range from 6 to 61 cGy/MBq (220-2260 rad/mCi) with a mean absorbed dose of 23 cGy/MBq (850 rad/mCi).

A dose estimation study was conducted by Breen *et al*. [46] on 4 patients with bone metastases from prostate cancer. The patients received first 37 MBq of ^{85}Sr-chloride and within 7 days a therapeutic injection of 150 MBq (4 mCi) of ^{89}Sr. The dosimetric method recommended by MIRD was used to estimate the average absorbed dose. After infinite time, the mean absorbed dose to metastatic lesions was 68 cGy/MBq (2519 cGy/mCi) with a range from (21±4) to (231±56) cGy/MBq. The absorbed dose delivered to red marrow was found to be less by a factor of about 2 to 50.

According to the ICRP Publication 53 [32], the mean absorbed dose to bone surface and to red bone marrow is 17 and 11 mGy/MBq (630 and 410 mGy/mCi), respectively. The calculations for bone surface and red bone marrow by GSF model [53] are 21 and 17 mGy/MBq (778 and 630 mGy/mCi), respectively. Consequently, these values are comparable to the values of ICRP model.

iv) Yttrium-90

Introduction

Yttrium-90 (^{90}Y) has been used in medicine since 1960, in order to treat various kinds of benign and malignant tumors. Since then, a great number of studies have been performed to evaluate the absorbed dose and the efficiency of all the radiopharmaceutical products that use this isotope.

Production and Physical Characteristics

^{90}Y is a pure β-emitter with a physical half-life of 64.1 h (2.67 days) and it decays to stable Zirconium-90 (^{90}Zr). The β-rays emitted by its decay have an average value of 0.9367 MeV while their maximum energy reaches 2.284 MeV. Its average range in tissue is about 2.5 mm and its maximum about 11 mm while the distance within which the β-partical transfers 95% of its energy to the target tissue is about R_{95}= 5.94 mm. Therefore, it is more suitable for therapeutic use and it has been measured that one GBq (27 mCi) of ^{90}Y delivers a total

absorbed radiation dose of 50 Gy/kg. In therapeutic use in which the isotope decays to infinity, 94% of the radiation is delivered in 11 days [54, 55].

^{90}Y can be produced by two different ways, depending on whether the specific activity is low or high. Low specific activity ^{90}Y is produced in a nuclear reactor by neutron activation of the non-radioactive ^{89}Y, when ^{89}Y captures a neutron and becomes the radioactive β-emitter ^{90}Y. This product is of very low specific activity, due to the small neutron capture cross-section of ^{89}Y, but its radionuclide purity is generally very high. For very high specific activity ^{90}Y (that is used for target therapy), a radionuclide generator system of Strondium-90 (^{90}Sr) is used and it is based on the fact that ^{90}Sr decays to ^{90}Y.

Four types of ^{90}Sr/^{90}Y generators have been developed: 1) Ion exchange based generator 2) Single stage SLM based generator 3) Two stage SLM based generator and 4) Electrochemical generator. The best of these generators is the electrochemical system as it yields around 97–98% of ^{90}Y deposition. Other advantages of this generator is that it is based on equilibrium, as the parent element is very long-living ($T_{sr1/2}$= 28.8 y) and it gives a short-living daughter ($T_{Y1/2}$= 64.1 h). In that way, a great quantity of pure and high specific activity ^{90}Y can be produced, with a small amount of ^{90}Sr for a great period of time. However, the installation of such generator in nuclear medicine departments is not easily realised because of the long-lived waste that require careful handling and storage [56, 57].

Uptake and Biokinetic Properties

One of the most widely used products for target therapy with radionuclides is the ^{90}Y-DOTA-[D-Phe1-Tyr3]-octreotide, used for the treatment of patients with progressive neuroendocrine tumours, cancers expressing somatostatin receptors [55, 58, 59]. In this radiopharmaceutical, a somatostatin analogue Tyr3-octreotide is a derivative with the chelator DOTA, enabling stable radiolabelling with the high-energy β-particle-emitting isotope ^{90}Y. The specific somatostatin analogue has a high affinity for somatostatin subtype receptors SSTR2 and SSTR5 [58, 60]. ^{90}Y-DOTA is also used for treatment of patients with pancreatic cancer. In this case, ^{90}Y-DOTA is radiolabelled with a humanized monoclonal antibody against mucin [61].

^{90}Y is a pure β-emitter, thus, ^{86}Y-DOTATOC, or ^{111}In-DOTATOC or even ^{111}In-DTPA-OC is used for quantitative imaging. ^{86}Y-DOTATOC requires a high-energy cyclotron and a (Positron Emission Tomography) PET facility but its major drawbacks are it's the short half-life (14.3 h) and the limited availability. On the other hand, ^{111}In compound presents some differences in its biodistribution comparing to ^{90}Y-DOTA-TOC. In all cases, the agent is localized primarily in spleen, kidneys and liver, and together with the urine bladder these organs get the highest absorbed dose, as the residence time of the product in these organs is notable [58-60, 62, 63].

Selective Internal Radiotherapy (SIRT) utilizes ^{90}Y microspheres. It is a palliative therapy with small spheres; these are injected into the human body, directly into the arterial supply of the liver, by using an appropriate port and a catheter, and they preferentially flow into hyper-vascularised tumour areas. It is used in cases of hepatic neoplasia and metastases as well as in metastatic colorectal cancer. ^{90}Y microspheres are point sources of radiation that preferentially localize in the peritumoural and intratumoural arterial vasculature [54, 64-67]. SIRT therapy takes advantage of the dual blood supply of the liver. The majority of hepatic tumours derive 80-100% of their blood supply from the hepatic artery. The concentration of spheres is greatest immediately adjacent to the boundary and falls away towards the interior of the tumour.

^{90}Y is a pure β-emitter and it can not be traced by means of scintigraphy. To resolve this problem ^{99m}Tc-labeled macro-aggregates of albumin (MAA) are injected as their particle size and biodistribution are comparable with those of ^{90}Y- microspheres [64-70].

Another use of ^{90}Y is in the treatment of non-Hodgkin's Lymphomas with the form of ^{90}Y-ibritumomab-tiuxetan. ^{90}Y is directed towards the tumour cells by creating a crossfire effect. This crossfire effect makes the radiation to penetrate bulky or poorly vascularised tumours and to expose the normal cells to minimum. In order to meet the imaging purposes, it is needed to inject ^{111}I-ibritumomab-tiuxetan [71, 72].

In case of non-small cell lung cancer, ^{90}Y-anti-TAG-72 murine antibody (^{90}Y-CC49) is used with ^{111}In-CC49 as a tracer. Great interest is shown on the red marrow absorbed dose, as it is the critical organ for myelotoxicity. Though this radiopharmaceutical is not gathered to the red marrow and the radiation contribution to marrow from tissues other than the skeletal is small in the case of radiolabelled antibodies, there is an amount of radiation that is transferred there by the blood [73].

Another use of ^{90}Y is as a postoperative intracavitary treatment for malignant glioblastoma, which is a relatively uncommon form of central nervous system (CNS) tumour. ^{90}Y is frequently labelled to BC-1, BC-2 or BC-4 monoclonal antibodies. A highly absorbed dose is then delivered to residual clonogenic cells while the damage to the surrounding normal structures is minimal [74].

Finally, for patients with rheumatoid arthritis (RA), that is unresponsive to glucocorticoids, nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatoid drugs, cronic oligo- or mono-arthritis can be treated by radionuclide synovectomy. Radiosynviorthesis with ^{90}Y is an established concept for the treatment of persistent synovitis of the knee joint [75, 76].

An attempt has also been made in order to treat the epithelial ovarian cancer with ^{90}Y-labeled murine HMFG1 after surgical debulking and chemotherapy; this approach failed, probably

because of limited transfer of β-emitters to the tumour by a single administration of ^{90}Y-muHMFG1 [77].

Dosimetry

As far as ^{90}Y-DOTATOC is concerned, a lot of research has been made in order to estimate and calculate the absorbed dose. Cremonesi *et al*. [60] and Paganelli *et al*. [55] calculated the absorbed doses for ^{90}Y-DOTATOC according to the MIRD formalism and they found similar results. The highest absorbed doses were to the spleen, the urinary bladder wall and the kidneys but there was a low risk of myelotoxicity. Tumour doses were high enough in order to accomplish the therapeutic response.

Förster *et al*. [58] and Helisch *et al*. [59] injected patients suffering from metastatic carcinoid tumours with [86]Y-DOTATOC and, later they re-investigated the same patients with conventional scintigraphy using ^{111}In-DTPA-octreotide. Absorbed doses were calculated by applying the MIRDOSE3.1 and IMEDOSE software. Hindorf *et al.* [78] measured the whole body absorbed dose of 30 patients with neuroendocrine tumours injected with 100MBq ^{111}In-DOTATOC and the absorbed dose to tumour and kidneys in 17 patients by using the MIRD scheme. The differences in reported dosimetry results for ^{90}Y-DOTATOC according to past research could possibly be explained by the fact that they were based on different radiopharmaceutical compound agents, different methodologies for kidney protection, different acquisition methodologies (whole-body counter, planar scintillation camera images, SPECT, and PET), different organ/tumour volumes (CT, magnetic resonance imaging, ultrasound, and standard MIRD phantom volumes) and, furthermore, they were based on a rather low number of patients. However, generally ^{90}Y-DOTATOC reported renal toxicity. Therefore, amino acid co-infusion during therapy has been established as a standard procedure in order to decrease radiation burden to the kidneys [59, 78]. The results of all four researches are included in Table 1.

[90]Y-microspheres have been used in medicine since 1960 and a lot of research has been performed in order to measure the absorbed dose of the tumour and the other organs of the human body. In the first decades, radiation doses to normal liver were frequently estimated using standard MIRD techniques based on the average energy deposited per mass of tissue. However, these methods assume that all the activity infused is delivered uniformly throughout the liver. In a period of time, more accurate techniques have been used in order to give as realistic results as possible.

Campbell *et al.* [79] measured the absorbed dose in liver and tumour area that comes from the injection of 3 GBq of ^{90}Y-microspheres. The absorbed dose was calculated by using custom software written in the C programming language (Borland C++ Builder v1.0). In this

program, each microsphere was assumed to act as a point source of radiation, while, the volume over which radiation doses were determined, was divided into a regular mesh. After appropriate calculations, made by computing the distance of the microsphere from the mesh point and using the beta dose point kernel for ^{90}Y to find the radiation dose rate at that distance, it has been resulted that microspheres have been deposited preferentially in tumour tissues, with a sharp delineation between tumour and normal liver tissues (approximately 200 times higher concentration in tumour periphery than in normal liver). In addition, microsphere concentration steadily declined towards the center of the tumour. The results from the calculations have shown that preferential deposition of microspheres in tumours leads to therapeutic doses for the tumour, while most of the normal liver tissue is spared substantial damage.

Table **1.** Organ absorbed dose for 90Y-DOTATOC based on different tracers.

	Estimated Absorbed Doses (mGy/MBq)					
Study	Cremonesi et al.*	Förster et al.**		Helisch et al.***		Hindorf et al.****
Organs	^{111}In-DOTATOC	^{111}In-DTPA-	^{86}Y-DOTATOC	^{111}In-pentetreotide	^{86}Y-DOTATOC	^{111}In-DOTATOC
Total Body	0.14±0.06	0.085±0.01	0.082±0.014	–	–	0.097 (0.038-
Red Marrow	0.03±0.01	0.042±0.00	0.049±0.002	0.06±0.02	0.06±0.03	–
Intestinal Tract	–	0.620±0.42	0.049±0.002	–	–	–
Liver	0.7±0.6	0.594±0.14	0.656±0.148	0.72±0.40	0.40±0.26	–
Kidneys	3.3±2.2	3.013±0.80	2.728±1.408	1.71±0.89	1.98±0.75	3.8 (1.9–7.6)
Spleen	7.6±6.3	2.786±1.53	2.320±1.970	2.19±1.11	3.31±1.02	–
Urinary Bladder	2.2±0.3	0.764±0.50	1.030±0.225	–	–	–
Other Tissue	0.08±0.04	0.042±0.00	0.049±0.002	–	–	–
Tumour Lesions	10.1 (1.4-31.0)	3.727 (0.96-7.76)	9.87 (3.21-19.58)	8.97±6.55	9.42±5.63	3.8 (0.9-5.4)

* Referred as [60], ** Referred as [58], *** Referred as [59], **** Referred as [78]

Sarfaraz *et al.* [65] used images from single-photon emission computed tomography (SPECT), after injection of 4.5 GBq of ^{99m}Tc-MAA, in order to derive the activity distribution within liver. Calculations with Monte Carlo have been performed to create a voxel dose

kernel for the ^{90}Y source. They have notified that if the activity were to be distributed uniformly within the liver, the radiation absorbed dose to the entire liver would be 110 Gy. However, only the 16% of the normal liver has received dose higher than 110 Gy, with a mean dose of 58 Gy, while in the case of tumour the 83% has received more than 110 Gy, with a mean dose of 163 Gy. Concerning the other organs, the maximum dose to right kidney was 25 Gy and to the stomach was 60 Gy.

Gulec *et al*. [67] studied forty patients with liver disease (CRC, HCC, neuroendocrine tumours (NET) and metastatic liver disease from various other malignancies) in which (1.2±0.5) GBq of ^{90}Y-microspheres (range from (0.4-2.4 GBq) were injected. Calculations of the absorbed doses have been made by using images taken after injection of ^{99m}Tc-MAA and the MIRD approach. The results of these calculations were that the mean absorbed dose for the tumour was (121.5±85.6) Gy, for the liver was (17.2±18.6) Gy and for the lungs was (2.1±2.3) Gy. No linear relationship was found between the administered activity and tumour absorbed dose. However, the liver absorbed dose increased with administered activity.

v) Indium-111

Introduction

Indium-111 (^{111}In) is radioisotope that was introduced for nerve endocrine tumour cancer cells diagnosis. It is also successfully used for nerve endocrine tumour radio-immunotherapy.

Production and Physical Characteristics

^{111}In is produced by cyclotron from ^{112}Cd collision with protons of energy 2.8 MeV according to the nuclear reaction ^{112}Cd(p,2n)^{111}In. The radioactive ^{111}In decays to ^{112}Cd with physical half-life time of 2.83 days. The type, energy and emission ratio for each decay are displayed at Table 2.

Purity of the final product of ^{111}In is affected by the undesired isotopes ^{110m}In, ^{110}In and ^{114m}In that are not possible to spare from ^{111}In due to the similar chemical characteristics of these isotopes [80].

The isotopes ^{110m}In and ^{110}In, do not affect dosimetry of radioisotopes labeled with ^{111}In, because these undesired isotopes have minor presence and small half-life time (4.9 h and 1.1 h, respectively). On the contrary, ^{114m}In that is produced from ^{114}Cd according to a (p,n) nuclear reaction, has 49.51 days half-life time and decays with internal transition (96.9%) and electron capture (3.2%) with emission of photons at 192, 558 and 725 keV. ^{114m}In affects dosimetry due to its long half-life time.

Table **2.** [111]In decay chart

Type of decay	Energy (keV)	Emission ratio (Bq·s)$^{-1}$
Photons	150.8	$3 \cdot 10^{-5}$
Photons	171.3	0.906
Photons	245.4	0.941
Electrons IT*	145 – 170	0.1
Electrons IT*	218 – 245	0.06
Electrons Auger	19 – 25	0.16
Electrons Auger	2.6 – 3.6	1.02
Electrons Auger	0.5	1.91

* IT, *Internal Transform*

Uptake and Biokinetic Properties

[111]In-octreotide is used for radio immunotherapy for nerve endocrine tumours of the gastro hepatic system. Octreotide is a somatostatin analogue used for labeling [111]In. Somatostatin is a peptide of the gastro enteric system that inhibits the production of the grow hormone. There is an over expression of the somatostatin receptors at the surface of the nerve endocrine tumour cancer cells. ^{111}In-octreotide is bounded to the somatostatin inhibitors and transferred into the cancer cell. Auger electrons that are emitted from ^{111}In can damage the DNA of the cancer cell [80-87].

Dosimetry

Dosimetry of ^{111}In-octreotide therapy can be performed with planar or tomographic scintigraphy images.

Table **3.** Comparison of Studies: Dose After Antecubital and Transhepatic Infusions

Study \ Organs	Kwekkeboom*	Krenning*	Fjälling*	Mallinckrodt*	Stabin*	Kontogeorgakos†
Kidneys	0.46	0.495	0.200	0.450	0.520	0.410
Liver	0.08	0.095	0.590	0.070	0.065	0.140
Spleen	0.32	0.380	0.350	0.320	0.340	1.400
Bone marrow	0.02	0.021	0.200	-	0.029	0.0032

*Antecubital Infusion, †Transhepatic Infusion

Measured count rate is converted into activity. Tumour and organ absorbed doses are estimated by the time-activity curves, according to the MIRD schema [88-98]. The mean absorbed doses for tumour, kidneys, spleen, pancreas and liver (liver excluding tumour metastasis) are 10.2, 0.13, 0.2, 0.003 and 0.002 mGy/MBq, respectively, as measured over tomographic scintigraphy images at Aretaieion Hospital, nuclear medicine department, for 8 patients. Table 3, published at Kontogeorgakos *et al.* [99] and been somewhat modified, presents some dosimetric results from various institutions.

vi) Tin-117m

Introduction

Tin-117m (^{117m}Sn) is a radionuclide utilized mainly in the treatment of primary or metastatic bone malignancies as well as in the pain palliation [100]. It is characterised by selective radiation dose delivery to the target as well as low toxicity and few long-term effects to other adjacent organs. In most cases, patients have experienced substantial pain relief.

Production and Physical Characteristics

Sn-117m can be produced by two processes. The first process includes the radiative neutron capture by the enriched nuclei of ^{116}Sn and the interaction is the following: ^{116}Sn $(n_{th},\gamma)^{117m}$Sn. The second process includes the inelastic scattering reaction of enriched ^{117}Sn nuclei following the interaction ^{117}Sn $(n_{fast},n'\gamma)^{117m}$Sn [101].

^{117m}Sn has a physical half-life of 13.6 days. It decays by isomeric transition with the emission of abundant (114%) low-energy monoenergetic internal conversion electrons with energy of 127, 129 and 152 keV [101, 102]. Due to the low energy of these electrons, they deposit their energy to a very short range in the tissue following a short path. The maximum and mean range of the 127 keV electron is 0.27 mm and 0.2 mm, respectively, while the mean range of the 152 keV electron is 0.3 mm [104]. These characteristics result in high *S* values and a desirable therapeutic outcome [105]. Moreover, ^{117m}Sn emits a gamma photon of energy 158.6 keV and intensity of 86% which contributes to the imaging of the distribution of the injected radiopharmaceutical as well as to the comparison with other bone imaging radiopharmaceuticals such as ^{99m}Tc-MDP [103].

Uptake and Biokinetic Properties

^{117m}Sn (4+)/DTPA (Diethylenetriaminepentaacetic Acid) is widely used for pain palliation in cases of bone cancer. In comparison to beta emitters, it presents a great advantage as higher

activities can be administered to patients for further alleviation due to its very low toxicity and low dose absorption in the bone marrow [106]. It does not follow the excretion route through urine that most radiopharmaceuticals do. Nevertheless, it concentrates almost exclusively into the bones and it remains there for a significant amount of time resulting in a good therapeutic outcome [105].

Several types of detection of the radiopharmaceutical distribution have been established. Swailem *et al.* [107] presented a study of the distribution of ^{117m}Sn (4+)/DTPA inside the human body. They use a gamma camera for the detection of the 158.6 keV photopeak performing whole body scans. According to that study, 137 hours after the injection there was a peak uptake in the lesion bones which had accumulated 66.8% of the injected activity while soft tissue had accumulated only 14.3%. The rest of the activity (18.9%) had been excreted via urine. Apart from this, it was shown that selective accumulation happened as significantly greater activity had been concentrated on the lesions and not on the healthy bones. Moreover, no clearance from the bones was observed for a prolonged period of time.

Another parameter included in the study of the biokinetics is the collection of blood and urine data at different intervals determining the toxicity to the blood components as well as the excretion of the radiopharmaceutical. Moreover, time-activity curves can be obtained determining the deposition of the agent to normal and lesion bone [108].

Dosimetry

Atkins *et al.* [109] studied 10 cases of metastatic bone cancer and worked on bone pain palliation using ^{117m}Sn (4+)/DTPA. They calculated the average absorbed dose of each organ for women and men separately using the MIRDOSE programme. For women, it was calculated that the bone surfaces received 71.621 mGy/MBq, the bone marrow received 6.567 mGy/MBq and the total body received 0.681 mGy/MBq of administered activity. For men, the absorbed dose was somewhat lower. The bone surfaces received 54.864 mGy/MBq, the bone marrow received 6.108 mGy/MBq and the total body received 0.535 mGy/MBq. All other organs received significantly lower dose, between 0.07 and 0.22 mGy/MBq for women and men, respectively.

Srivastava *et al.* [110] presented a study in which forty-seven patients suffering from bone metastasis of different origin where treated with ^{117m}Sn (4+)/DTPA. In seven patients, the absorbed dose to bone surfaces and bone marrow was calculated, using MIRDOSE3 programme, and they found 63.2, 12.6 cGy/37 MBq (or rad/mCi) for women and 65.1, 9.8 cGy/37 MBq (or rad/mCi) for men for bone surfaces and bone marrow, respectively. According to Krishnamurthy *et al.* [108], the normal bone radiopharmaceutical attach was about half of that attached on the lesion bone.

McEwan [111] presented a comparison of the absorbed dose from different radiopharmaceuticals. According to this study, the dose fluctuates depending on some factors and bones receive 54-81 mGy/MBq, bone marrow receives 3.2-7.3 mGy/MBq and the bladder receives 0.16 mGy/MBq.

Consequently, this radioisotope gives the best bone to marrow ratio compared to other ones used for bone therapy [112]. It also presents a great advantage over the beta-emitter radioisotopes in the overall dosimetry.

vii) Iodine-131

Introduction

More than 50 years (in the 1930s and 1940s) have passed since Radioactive Iodine Therapy (RIT) was introduced for treating hyperthyroidism caused by Graves' disease [113]. Many physicians avoid this highly effective therapeutic option in favour of prolonged treatment with antithyroid medication or surgery. There is a report detailing favourable outcomes nearly four decades after children and adolescents received radioactive Iodine treatment. In this, it is suggested that fears of radioactive Iodine use in children do not stand on strong legs [114]. In the 1960s and 1970s, several groups reported their experience using radioactive Iodine to treat childhood Graves' disease [115-121]. Today, it is used in nuclear medicine both diagnostically and therapeutically. In therapy, it is used for treatment for an overactive thyroid, a condition called hyperthyroidism. RIT is also used to treat different types of thyroid cancer [122].

Production and Physical Characteristics

^{131}I is a β-emitting radionuclide with a physical half-life of 8.1 days, a principal γ-ray of 364 KeV and a principal β-particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. Therapy with I-131 means the oral administration of I-131 as sodium iodide. Malignant conditions include thyroid cancer that is sufficiently differentiated to be able to synthesize thyroglobulin and, in most cases, accumulate radioiodine [124].

^{131}I is a fission product of ^{235}U along with a lot of others. The fission cross-section is highest for thermal neutrons (E~0.0253 eV). ^{131}I is also a decay product of ^{131}Te (fission product of ^{235}U) and decay product of ^{131}Sb. ^{131}Te can be formed by neutron capture of ^{130}Te, but that presents very low probability. Neutron capture by ^{130}Te would probably be the best way to produce ^{131}I. On decaying, ^{131}I transforms into the stable ^{131}Xe by emitting beta radiation. ^{131}I

is produced by the irradiation of Tellurium-130 in a nuclear reactor according to the reaction: ^{130}Te (n,γ)^{131}Te→^{131}I.

In medical applications, ^{131}I is added to NaOH solution containing 0.02 M Na2SO4 with pH=9.0-12.0. Its activity concentration usually is equal or higher than 1000 mCi/mL (for high concentration) and 200-1000 mCi/mL (for low concentration). As for its radiopurity, it is usually equal or higher than 99.9% [123].

Uptake and Biokinetic Properties

For hyperthyroid patients, one method is to use the estimated thyroid gland size and the results of a 24-h RAIU test to calculate the amount of ^{131}I to administer in order to achieve a desired concentration of ^{131}I in the thyroid gland. Delivered activity of 2.96-7.40 MBq (80-200 µCi) per gram of thyroid tissue is generally appropriate. The thyroid radiation dose depends on the RAIU as well as the biological half-life of the radioiodine in the thyroid gland. The biological half-life can vary widely.

For thyroid cancer patients, a variety of approaches have been used to select the amount of administered activity. General guidelines are listed below:

a. For postoperative ablation of thyroid bed remnants, activity in the range of 2.75-5.50 GBq (75-150 mCi) is typically administered, depending on the RAIU and amount of residual functioning tissue present.

b. For treatment of presumed thyroid cancer in the neck or mediastinal lymph nodes, activity in the range of 5.55-7.40 GBq (150-200 mCi) is typically administered.

c. For treatment of distant metastases, activity higher than 7.4 GBq (200 mCi) is often given. The radiation dose to the bone marrow is typically the limiting factor.

However, in 20-30% of incidents, radioactive iodine is not accumulated in the thyroid gland resulting in poor diagnosis or therapy. Thus, other methods can be utilized including the maximization of the administered activity and the use of retinoic acid to achieve re-differentation of the cancer cells [125]. Oral administration of lithium carbonate prolongs the intrathyroidal biological half-life of administered ^{131}I and occasionally may be useful in patients who have a rapid turnover of radioactive Iodine. Serum Lithium levels should be monitored to avoid toxicity. A short effective ^{131}I half-life can be a source of failure of ^{131}I therapy in metastatic lesions. Side effects may occur and are generally dose related.

Patients should have whole body scintigraphy approximately 3-14 d after treatment for staging purposes. They are required by the NRC to remain in the hospital if any individual member of the public is likely to exceed a radiation dose of 5 mSv from that patient. Since the overall recurrence rate for thyroid cancer approaches 20%, and up to 10% of recurrences occur after twenty years, long term follow-up of the patient is recommended, both to maintain suppressed serum TSH levels (kept below normal but at or above about 0.1 uU/mL to reduce

the risk of osteoporosis and atrial fibrillation) and to detect new sites of thyroid cancer [32, 126].

Dosimetry

For the dose determination, Monte Carlo codes are utilized. In one study [127], determination of the total body absorbed dose consists of two parts: beta radiation absorbed dose and gamma radiation absorbed dose. The first part is generally determined by clinical data, while the second part has a parameter called absorbed ratio and is determined by computational methods. The Monte-Carlo computational methods have been shown to be the most suitable in determination of the absorbed dose ratio. The Monte-Carlo code MCNP-4A was employed in order to calculate the absorbed ratio for the whole body and thyroid gland. The distributed source of ^{131}I was used to calculate the absorbed ratio for emitted photons in different energies from this source, within an ellipsoid phantom having the human body dimension. Water and material similar to body tissue were chosen as the phantom's filling materials.

The accuracy of dosimetry calculations in internal emitter therapy applications is often limited by a lack of data describing the time dependence of the spatial activity concentration in patients. In many cases, time-dependent activity data is acquired only for specific regions of interest (ROIs) and measurements of patient anatomy and 3D activity distributions are made at only single time points during tracer studies. When calculating absorbed dose in these applications, this scarcity of data necessitates the approximation that activity distributions can be wholly defined by single spatial measurements, and that all points within given ROIs exhibit uniform time dependence [128].

In many studies, CT and SPECT images have been acquired using a dual-modality scanner at multiple time points after administration of both tracer and therapy activity to follicular lymphoma patients being treated with ^{131}I. The data has been registered to a single CT image and the mutually registered SPECT images have been used to derive integrated time-activities on a voxel-by-voxel basis. Maps of integral time-activity have been used in conjunction with CT images to determine 3D absorbed dose distributions by Monte Carlo computation. Usually, results are presented by illustrating the differences between calculations of spatial distributions of integrated activities and absorbed doses made with the current technique and those performed with previous methods [128].

In another study, SPECT quantification included three-dimensional (3D) ordered-subset expectation-maximization (OSEM) reconstruction with CT-defined tumour outlines at each time point [129]. SPECT/CT images from multiple time points were coupled to a Monte Carlo algorithm to calculate a mean tumour dose that incorporated measured changes in tumour volume. The tumour shrinkage, defined as the difference between volumes drawn on the first and last CT scan (a typical time period of 15 days) was in the range 5-49%.

The *in vivo* distribution and kinetics of [^{131}I]Ethiodol injected through the hepatic artery have been measured on four patients suffering from hepatocellular carcinoma [130]. The [^{131}I]Ethiodol was distributed predominantly in the liver (70–90%) and lungs (10–20%) and was selectively concentrated and retained in the patients with massive and multinodular hepatomas, with 10% of the administered activity localizing in tumour.

As for the internal dosimetry of ^{131}I in patients with thyroid carcinoma in the Instituto Nacional de Cancerologia, Bogota-Colombi, a patient-specific dosimetry protocol was developed and applied, using the administration of a tracer amount of this radionuclide and the methodology of the MIRD [131]. The dosimetry method consists of a determination of the maximum tolerated activity that will deliver 2 Gy to the blood and the corresponding ablative lesion dose. The internal dosimetry is useful in determining the optimal amount of administered activity in radioiodine therapy, so that the absorbed doses to the organs of interest proved to be the optimal, without overcoming the maximum tolerated dose in the red marrow and the lungs.

viii) Samarium-153

Introduction

Prior to the advent of ion-exchange separation technology in the 1950s, Samarium had no commercial use in pure form. However, a by-product of the fractional crystallization purification of neodymium was a mixture of Samarium and Gadolinium that acquired the name of "Lindsay Mix" after the company that made it. This material is thought to have been used for nuclear control rods in some of the early nuclear reactors. Nowadays, a similar commodity product has the name "Samarium-Europium-Gadolinium" (SEG) concentrate [135]. It is prepared by solvent extraction from the mixed lanthanides extracted from bastnäsite (or monazite). Its purification follows the removal of the Europium. Currently, being in oversupply, Samarium oxide is less expensive on a commercial scale than its relative abundance in the ore might suggest.

Production and Physical Characteristics

Samarium (Z=62) is a rare earth metal (lanthanide), found in Row 6 of the periodic table, with a bright silver luster. Three crystal modifications of the metal also exist, with transformations at 734 and 922 °C, making it polymorphic. Individual samarium atoms can be isolated by encapsulating them into fullerene molecules [133]. Samarium oxidizes in air and ignites at 150 °C. Even with long-term storage under mineral oil, samarium is gradually oxidized, with

a grayish-yellow powder of the oxide-hydroxide being formed [134]. The metallic appearance of a sample can be preserved by sealing it under an inert gas such as argon. Samarium has the following physical characteristics: melting point at 1.072°C (1.962°F), boiling point at 1.900°C (3.450°F), density approximately 7.53 g/cm^3. Moreover, radionuclide of Samarium-153 (^{153}Sm) is produced by neutron capture of isotopically enriched ^{152}Sm$_2$O$_3$. Physical characteristics such as half-life of 46.27 h with beta emission energy at 0.64, 0.71 and 0.81 MeV and gamma emission at 0.103 MeV make it a radionuclide of choice.

Uptake and Biokinetic Properties

^{153}Sm lexidronam (chemical name Samarium-153-ethylene diamine tetramethylene phosphonate, abbreviated ^{153}Sm-EDTMP) is a complex of a radioisotope of the radionuclide ^{153}Sm with the chelator EDTMP which is widely used as a palliative treatment for painful skeletal metastases [136, 137]. It is perspicuous, colorless with a pH between 7.0 and 8.5. The widely used administered activity of ^{153}Sm-EDTMP is 37 MBq/kg of the patient. It is injected into a vein and distributes throughout the body. It homes in on metastatic lesions. Once there, the radioisotope emits beta particles which kill the nearby cancer cells. Pain begins to improve in the first week for most people and the effects can last several months [138]. It is commonly used in osteosarcoma caused in immature individuals [139] and more rarely in lung, prostate and breast cancer treatment. Side effects on the bone marrow, resulting from radiation, must be taken into account because there is a threat of thrombocytopenia and leucopenia [140]. ^{153}Sm-EDTMP is rapidly eliminated through bloodstream and urinary system. The total uptake of metastatic lesions is about (65.5±15.5)% of the administration dose and it is proportional to the number of skeletal metastases.

Dosimetry

Bayouth *et al*. [141] followed the usual protocol of ^{153}Sm-EDTMP administration (0.5-37 MBq/kg of patient) and the mean skeletal uptake for all 19 patients was found (54%±16)% of the injected dose (%ID). This resulted in the bone marrow dose of (0.89±0.27) mGy/MBq. The dose calculations were undergone, using MIRD formalism.

As Maini *et al*. [142] regard upon injection of ^{153}Sm, more than 50% of the dose is avidly fixed by lesional and non-lesional bone with the rest being rapidly eliminated unchanged via urine. For a standard dose of 37 MBq/kg (1 mCi/kg), which is proven to be more efficient than the substitutional dose of 18.5 MBq/kg (0.5 mCi/kg), the estimated radiation dose to metastases is about 33 mGy/MBq. Critical organs such as bladder wall and red marrow received 0.97 mGy/MBq and 1.54 mGy/MBq, respectively.

In Lagopati *et al*. [143] method, skeletal metastasis lesion doses were ranging from 23 to 34 mGy/MBq. Marrow doses ranged from 1.2 to 2.0 mGy/MBq and urinary bladder doses

ranged from 0.83 to 0.12 mGy/MBq, calculated by MIRDOSE 3.1, using MIRD schema for an individualized dosimetry. Non-skeletal sites received negligible doses. According to Monte Carlo simulation, lesion dose was fluctuating between 26 and 37 mGy/MBq. In order to compare the absorbed dose in the metastatic lesion area to the equivalent in critical organs, the Dose Index (X) ratio is used: $X = D_{lesion\ area}/ D_{critical\ organ}$, where $D_{lesion.area}$ refers to the absorbed dose in the metastatic lesion and $D_{critical.organ}$ refers to the absorbed dose in the critical organ (red marrow and bladder).

Eat *et al*. [140] declare that a standard clinical routine, with a patient specific calculation of dose, results to negligible doses at non-skeletal sites. However, the skeletal uptake fluctuates between 5.3 and 8.8 mGy/MBq, marrow doses range from 1.2 to 2.0mGy/MBq and urinary bladder doses range from 0.36 to 1.30mGy/MBq.

The methods that are at the pin of nuclear medicine science, nowadays, presented in many publications and reviews are based on patient specific dosimetry in parallel to a long list of simulation codes such as FLUKA and GATE. The whole procedure results in a better dose estimation leading to a more efficient treatment plan.

ix) Holmium-166

Introduction

Holmium-166 is a radiolanthanide isotope that has been proposed for use in the treatment of resistant multiple myeloma [144] as well as hepatocellular carcinoma due to its physical and chemical characteristics. A number of studies and clinical trials have been performed in order to evaluate the contribution of this isotope to cancer radionuclide therapy.

Production and Physical Characteristics

^{166}Ho can be readily produced in a low or medium flux nuclear reactor through neutron bombardment of ^{165}Ho (monoisotopic in nature) following the interaction ^{165}Ho (n,γ)Ho^{166}. Natural Ho(NO$_3$)$_3$ can be used as a target material. The physical half-life of ^{166}Ho is 26.8 h. It is a β-emitter resulting in two principal β-emissions, at 1.85 MeV (51%) and at 1.77 MeV (48%). The mean energy of the β-particles' emissions is 711 keV. It also emits low yield γ-photons with energies of 80.6 keV (6.6%) and 1.38 MeV (0.9%). The two β-emissions attribute to a mean range of 4 mm and a maximum range of 8.7 mm in soft tissues [145, 146]. The photon emission can be conveniently used for imaging purposes by utilising a gamma camera, Medium Energy General Purpose (MEGP) collimator and a 15% photopeak window [147]. Besides ^{166}Ho, ^{166m}Ho is also produced from the above interaction having physical half-life of 1200 years and γ-emissions of 810 keV (57%) and 712 keV (54%) [148].

Uptake and Biokinetic Properties

[166]Ho can be attached to several agents for bone or liver cancer therapy. The most widely utilized radiopharmaceutical for bone therapy is [166]Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP) [149] which has been used for several years. However, different radiopharmaceuticals have been proposed for the treatment of liver cancer. The more widely known are the percutaneous [166]Ho/chitosan complex injection (PHI) [150], the [166]Ho-oxine-lipiodol complex [151] and the [166]Ho/poly lactic acid microspheres [146]. In all cases, the patient is hydrated in order to accelerate the clearance of activity.

[166]Ho-DOTMP has a selective skeletal uptake due to the nature of its agent and can deliver high amounts of dose to the bone marrow and trabecular bone [144]. It is slowly administered by a Hickman catheter. It is quickly excreted from the body via kidneys and urine. The average radioactivity amount can be 74 GBq (2 Ci) and the exact amount can be extracted through various factors [150].

[166]Ho/chitosan complex consists of a radiopharmaceutical which concentrates on the liver for the treatment of hepatocellular carcinoma. Chitosan is a h-1,4-linked polymer of 2-deoxy-2-amino-Dglucose derived from the deacetylation of chitin. The solution is injected percutaneously directly into the tumour with the simultaneous guidance of an ultrasound [152].

[166]Ho/poly lactic acid microspheres are radioactive particles which are administered through the right femoral artery to the hepatic artery via catheterisation. They have different diameter depending on the production company and the clinical use. Nijsen *et al*. [146] utilized microspheres with diameter between 20 and 50 μm while Wente *et al*. [153] utilized microspheres with mean diameter of 30 μm.

Dosimetry

Many dosimetric studies have been conducted for bone therapy. Rajendran *et al*. [150] presented a study in which 23 patients suffering from multiple myeloma were treated with [166]Ho-DOTMP. According to this study, an initial trace dose of 1110 MBq (30 mCi) was administered for the estimation of the absorbed dose by various organs. Whole-body counts as well as gamma camera images were obtained at different time intervals to determine the residence time. Using the MIRD model and the MIRDOSE3 algorithm, it was calculated that bone marrow received 0.54 mGy/MBq (0.02 Gy/mCi), urinary bladder received 0.54 mGy/MBq (0.02 Gy/mCi), bone surface received 0.81 mGy/MBq (0.03 Gy/mCi), kidneys received 0.0135 mGy/MBq (0.0005 Gy/mCi) while the whole body absorbed dose was 0.054 mGy/MBq (0.002 Gy/mCi).

Breitz *et al*. [149] presented a multicenter study with 12 patients suffering from the same disease. The treatment was implemented using [166]Ho-DOTMP. Using MIRD formula and the MIRDOSE3 algorithm, they calculated the absorbed dose to all organs. Taking the highest dose values, the bone marrow received 0.517mGy/MBq, the urinary bladder received 0.291 mGy/MBq, the bone surface received 0.920 mGy/MBq, the kidneys received 0.045 mGy/MBq and the whole body received 0.062 mGy/MBq. The rest of the organs received a dose between 0.013 and 0.014 mGy/MBq.

According to Bayouth *et al*. [154], 6 patients suffering from multiple myeloma were treated with [166]Ho-DOTMP, receiving different activity, from 0.519 to 2.1 Ci. Using the MIRD model and the MIRDOSE2 algorithm, the bone marrow dose was found to be between 0.405 and 0.865mGy/MBq.

For liver therapy dosimetry, the references in the bibliography are limited. Some studies have been performed in pigs. According to Konijnenberg *et al*. [155] the radiation dose to the pig liver was calculated after the administration of 500 MBq [166]Ho microspheres. MIRD, MCNP and PK models were utilized and it was found that the average absorbed dose was (11±2) mGy/MBq, (10±4) mGy/MBq and (10±4) mGy/MBq for each model, respectively.

x) Lutetium-177

Introduction

Lutetium-177 (^{177}Lu) has found a variety of applications in biomedical fields. Its main usage is in the treatment of neuroendocrine tumours but its applicability in the treatment of colon cancer, metastatic bone cancer, non-Hodgkin's lymphoma, lung, ovarian, prostate cancer, and gastroenteropancreatic tumours has also been studied.

Production and Physical Characteristics

[177]Lu can be directly produced with a relatively high specific activity by neutron activation of [176]Lu. Enriched target material is required for this production route since the natural abundance of [176]Lu is only 2.6%. As an alternative production route, ^{177}Lu can be obtained as carrier-free from beta decay of [177]Yb produced by neutron activation of [176]Yb (indirect production). Again, enriched target material is required but it may be recycled since the neutron capture cross section is only 2.4 b so resulting in negligible burn-up of [176]Yb. The direct production route is obviously more attractive; however, most of the medical applications require ^{177}Lu of high specific activity. Such product can be prepared at many reactors only by the indirect production route. [177]Lu with half-life of 6.71 days turns into the stable Hafnium-177 ([177]Hf). It emits beta radiation with a maximum energy of 498 keV and

low energetic gamma rays of 208 and 113 keV with 10% and 6% abundance, respectively, which enables direct monitoring of the activity distribution in patients' body with a gamma camera and subsequent dosimetry [156].

Uptake and Biokinetic Properties

^{177}Lu is most commonly used for the treatment of metastasised neuroendocrine Gastro-Entero-Pancreatic (GEP) tumours when it is labelled with [^{177}Lu-DOTA0,Tyr^3]octreotide known as ^{177}Lu-DOTATOC and [^{177}Lu-DOTA0,Tyr^3]octreotate known as ^{177}Lu-DOTATATE. According to Esser *et al*. [157], the biodistribution pattern for the two peptides is nearly the same. However, the residence time of radioactivity in the tumours is significantly longer in patients after ^{177}Lu-DOTATATE delivery. Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean ratio of the tumour residence time was 2.1. Similarly, the residence times in the spleen and the kidneys are significantly longer for ^{177}Lu-DOTATATE. Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean ratio of the residence time was 1.5 for spleen and 1.4 for kidneys.

Apart from the use of ^{177}Lu in neuroendocrine tumours, ^{177}Lu–EDTMP and ^{177}Lu–DOTMP are potential agents for palliative radiotherapy for bone metastasis. Biodistribution studies in animals show significant skeletal accumulation and retention, rapid blood clearance and insignificant uptake in the major organs/tissue. However, data in humans are not yet available [156, 159].

Dosimetry

Sandström *et al*. [160] studied the feasibility and reliability of individualized dosimetry in patients undergoing therapy based on SPECT in comparison to conventional planar imaging (using ROIs) with ^{177}Lu-DOTA-D-Phe^1-Tyr^3-octreotate (^{177}Lu-DOTATATE). Attenuation-corrected SPECT data were analyzed both by using organ-based volumes of interest (VOIs) obtaining the total radioactivity in the organ and by using small VOIs measuring the tissue radioactivity concentration. Absorbed doses in non tumour-affected kidney, liver and spleen were calculated and compared for all three methods (planar imaging, SPECT organ VOIs, SPECT small VOIs). When comparing the results of the absorbed doses derived from the calculation according to MIRD and OLINDA, respectively, the differences were in the range 0.5-4.5%. The results of this study are that planar and SPECT dosimetry is comparable in areas free of tumours but, due to overlap, the planar dosimetry highly overestimates the absorbed dose in organs with tumours. Furthermore, SPECT dosimetry based on small VOIs proved to be more reliable than whole-organ dosimetry.

In their study, Wehrmann *et al*. [161] compared the dosimetric parameter uptake, half-life (kinetics), mean absorbed organ and tumour doses of ^{177}Lu DOTANOC and ^{177}Lu

DOTATATE in 69 patients with neuroendocrine tumours and high somatostatin receptor expression. Dosimetric calculations were performed according to the MIRD scheme and they showed that ^{177}Lu-DOTANOC has a higher uptake for whole-body and normal tissue, as compared to ^{177}Lu-DOTATATE, leading to a significant higher whole-body dose of 0.07 mGy/MBq compared to 0.05 mGy/MBq of DOTATATE. Renal and spleen uptake as well as radiation doses were not significantly higher for DOTANOC. The uptake in tumour lesions and the mean absorbed tumour dose were higher for DOTATATE. The red marrow dose was approximately 0.2 Gy.

Forrer *et al*. [162] compared ^{177}Lu-DOTATOC with ^{90}Y-DOTATOC for the treatment of metastatic neuroendocrine tumours. For dosimetric calculations, ROIs were drawn manually on the whole-body scans from anterior and posterior projections. The parts of the kidneys showing tumour infiltration or superimposition were excluded from the evaluation of organ uptake. The Odyssey XP program (Philips Electronics N.V.) was used. Background regions were placed close to the ROIs for background correction. The geometric mean value between anterior and posterior was taken and corrected for attenuation and physical decay. Whole-body activity acquired immediately after injection was defined as 100% of the injected activity. Data was expressed as percentage of injected activity and aa a function of time. All patients were injected with 7,400 MBq of ^{177}Lu-DOTATOC. The resulting time–activity data were fitted to a monoexponential curve for the whole-body clearance and to a biexponential curve for the kidneys to calculate residence time. Published radiation dose factors were used to calculate the absorbed doses. The dose to the red marrow was calculated from the residence time in blood – assuming no specific uptake, a uniform distribution of activity and clearance from red marrow – equal to that from blood. The mean absorbed doses were (413±159) mGy for the whole body, (3.1±1.5) Gy for the kidneys, and (61±5) mGy for the red marrow.

Kwekkeboom *et al*. [163] studied the dosimetry of ^{177}Lu-octreotate (DOTATATE) by utilising the MIRDOSE3 package and they compare it with [^{111}In-DTPA0] octreotide (^{111}In-DOTATOC) which is the most popular radiopharmaceutical for neuroendocrine tumours. The injected doses of ^{177}Lu-DOTATATE and ^{111}In-DOTATOC in patients were 1,850MBq (50mCi) and 220MBq (6mCi), respectively. The absorbed doses for kidneys, liver, spleen and bone marrow were 610cGy/ 3,700MBq, 80cGy/ 3,700MBq, 800cGy /3,700MBq and 26cGy /3,700MBq, respectively. The highest tumour doses because of the high tumour uptake of ^{177}Lu-DOTATATE (3-4 times higher tumour uptake than with ^{111}In-octreotide) in this model are achieved with ^{177}Lu-octreotate, especially in smaller tumours.

xi) Rhenium-186

Introduction

The use of Rhenium-186-hydroxyethylidene diphosphonate (^{186}Re-HEDP) in bone pain palliation from multiple metastases has been proved to be highly justified and efficient. It is used for palliation because no single approach has been shown to prolong life. Advances in imaging enable us to evaluate the spatial distribution of radioactivity in tumours and normal organs over time [164]. ^{186}Re-HEDP is the most usually used as a bone-seeking radiopharmaceutical in patients with bone metastases originating from breast or prostate cancer with regard to toxicity, pharmacokinetics and bone marrow dosimetry as well as the palliating effect on bone pain [165].

^{186}Re-HEDP was first developed at the University of Cincinnati. HEDP is strongly adsorbed on hydroxyapatite *in vitro*. *In vivo*, it is markedly concentrated on primary and metastatic bone lesions. In 1979, there was a first suggestion as a possible use of ^{186}Re in the treatment of osseous metastases [166]. However, it took until 1986 to generate therapeutically useful bone-seeking compounds, when Deutsch and Maxon were able to purify the ineffective mixture originally reported by Mathieu [167].

Bone-seeking radiopharmaceuticals have traditionally been used to image tumours in bone, but, depending on the carrier ligand and the energy of the radioactive label, these agents can also be used to treat primary or metastatic tumours in bone [168].

Production and Physical Characteristics

^{186}Re is currently available from neutron irradiation of ^{185}Re in low specific activity, although progress has been made toward improvement [168]. High specific activity ^{186}Re can be produced by proton bombardment of enriched tungsten targets [166, 168-172]. However, there are large discrepancies in the literature about the excitation function of the ^{186}W (p, n)^{186}Re reaction [170, 172, 173].

In order to better assess the feasibility of producing multi-mCi levels of ^{186}Re for therapeutic applications via the ^{186}W (p, n) ^{186}Re reaction, the excitation function was re-measured. Cross sections for the production of ^{186}Re from natural tungsten have been measured using the stacked foil technique for proton energies up to 17.6 MeV [174].

^{186}Re-HEDP is a mainly beta-emitting radionuclide with a physical half-life of 89.3 h (3.78 d). Its main beta-emissions have maximum energies of $E_{max,1}$=1.077 MeV (71%) and $E_{max,2}$=0.939 MeV (22%), respectively. Along with the beta-emissions there is a gamma-emission of energy E_γ=137 keV (9%), as well, enabling molecular scintigraphic imaging during therapy and biodistribution assessment for patient–specific dosimetry calculations.

Recent studies have shown that [186]Re is emerging as an optimal candidate for radioimmunotherapy [175, 176]. This happens due to its nearly ideal half-life of 3.72 days as well as its decay properties (β^- and γ-rays characteristics). The energy deposited to cells suggests that [186]Re is a promising candidate for therapy of tumours from millimeter to centimeter dimensions [177].

Uptake and Biokinetic Properties

A sensitive and well-established method of bone uptake quantification is measurement of whole-body retention at 24 h after injection but since soft-tissue retention of diphosphonates is known to be as high as 30% of whole-body retention, it seems appropriate to measure soft tissue retention and net bone uptake [170].

In order to measure the bone uptake, scintigraphic images were taken in a sequence 24h to 5 days post administration. The relatively short physical half-life combined with the beta emissions allows the delivery of relatively high dose rate within a short period of time in areas of concentration. Furthermore its short half-life not only makes [186]Re-HEDP capable of administration on an outpatient basis, but also reduces the problems of radioactive waste handling and storage. The mean skeletal uptake was about 55% of the injected dose.

Dosimetry

Patient-specific, 3D-image based internal dosimetry involves the use of patient's own anatomy and spatial distribution of radioactivity over time to obtain an absorbed dose calculation that provides as output the spatial distribution of absorbed dose. The results of such a patient-specific 3D imaging-based calculation can be represented as a 3D parametric image of absorbed dose, as DVHs over user-defined ROIs or as the mean (or range) of absorbed doses over such regions.

A number of groups have pursued and contributed to 3D imaging-based patient-specific dosimetry. Several efforts utilized the basic MIRD formalism as applied to a standard phantom geometry. The standard phantom geometry was modified to include on-line Monte Carlo calculation and therefore the ability to introduce tumours and adjust organ masses and shapes. Voxel models introduced during the last two decades are derived mostly from (whole body) medical image data of real persons instead of the older mathematical 'MIRD-type' body models.

For internal dosimetry of photons and electrons, the parameters influencing the organ doses are mainly the relative position of source and target organs (for photon organ cross-fire) and organ mass (for organ self-absorption). As a consequence of these findings, the ICRP decided to use voxel phantoms being the current state of the art for the update of organ dose

conversion coefficients that will follow the forthcoming revision of the ICRP Recommendations.

According to the ICRP philosophy, these voxel phantoms should be representative of the male and female reference adult with respect to their external dimensions, organ topology and masses. To meet these requirements, voxel adult reference models of a male and a female have been constructed at the GSF, based on the voxel models of two individuals whose body height and weight resembled the ICRP reference values [174, 178]. The skeleton is a highly complex structure of the body, composed of cortical bone (CBV), trabecular bone (TBV), red bone marrow (RBM), yellow bone marrow (YBM), cartilage and endosteum ('bone surfaces').

The internal dimensions of most of these tissues are clearly smaller than the resolution of a normal CT scan and, thus, these volumes cannot be segmented in the voxel models. Therefore, the skeletal dosimetry has to be based on the use of fluence-to-dose response functions that are multiplied with the particle fluence inside specific bone regions to give the dose quantities of interest to the target tissues [179].

For the skeleton, the target tissues participating in dose calculations are the endosteum (formerly called 'bone surfaces') and the RBM. For radionuclides accumulating in the skeleton, the following source tissues are needed additionally: cortical bone, trabecular bone and YBM.

However, the dimensions of the trabecular, the cavities containing bone marrow and the endosteum layer lining these cavities, are clearly smaller than the resolution of a normal CT scan and, thus, these volumes could not be segmented in the voxel models [178, 179].

In another study [176], dose measurements were conducted in 27 men with progressive androgen-independent prostate cancer and bone metastases. Administered activities ranged from 1251 to 4336 MBq (33.8-117.2 mCi). Antitumour effects were assessed by post-therapy changes in prostate-specific antigen and, when present, palliation of pain. Whole-body kinetics, blood and kidney clearance, skeletal dose, marrow dose and urinary excretion of the isotope were assessed. Targeting of skeletal disease was observed over the period of quantification (4-168 h). Radiation doses to whole body, bladder and kidney were well tolerated. The determination of total activity retained at 24 h as well as an estimate of marrow dose, correlated with the amount of myelosuppression, was observed. Repetitive dosing is required to increase palliation.

Gamma-camera images (whole-body scintigrams and SPECT) of radiopharmaceutical distribution, in patients injected with ^{186}Re-HEDP, were analyzed to measure activity in specifically selected normal and metastatic regions of interest [165]. Calculations based on the MIRD schema, gave values of absorbed dose per unit volume (voxel) for metastatic and normal bone tissue, for all the radiopharmaceuticals studied.

Further analysis of these values leads to calculations of two important parameters: metastatic/normal bone absorbed dose ratio (M/B ratio) and bone/red marrow mean absorbed dose ratio (B/RM ratio). M/B ratio provides valuable information in assessing tumour-control probability, normal tissue toxicity and radiopharmaceuticals' qualification and superiority whereas B/RM ratio displays the red marrow toxicity induced by the radiopharmaceutical, a key issue for the success of the radiopharmaceuticals' therapeutic use.

Utilization of SPECT radionuclide distribution in defined ROIs can provide, through voxel slices, accurate foci volume and the dose rate calculations are performed for each lesion volume. For the evaluation of the spots volume estimation, cylindrical and spherical phantom of various known volumes could be used.

xii) Rhenium-188

Introduction

Rhenium-188 (^{188}Re) is an attractive radioisotope because of its physical properties and its production *in situ* by a ^{188}W/^{188}Re generator. ^{188}Re obtains a variety of therapeutic applications. The most predominant application is in bone palliation while it is also used in the treatment of liver tumours and non-Hodgkin's lymphomas. Experimentally, it has been also used for endovascular brachytherapy and treatment of ovarian and breast tumours.

Production and Physical Characteristics

The production of ^{188}Re can be employed by two reactions in nuclear reactor. The first reaction is: ^{187}Re→^{188}Re→^{188}Os (stable) while the second one is: ^{186}W→^{187}W→^{188}W (69.4 d, β^--emission) → ^{188}Re (16.9 h, β^--emission)→^{188}Os (stable). In ^{187}Re(n,γ)^{188}Re reaction, the target is metallic rhenium or oxide in natural abundance or enriched in ^{187}Re. Due to the high costs of the enriched target material this reaction has no importance for the routine production. Rhenium-188 has a significant advantage as it can be obtained by a Tungsten-188/Rhenium-188 generator system. Thus, the known benefits of the generators can be used. The parent radionuclide ^{188}W, formed by the double neutron capture on ^{186}W with β-decay, produces ^{188}Re which decays an energetic beta- particle with a maximum energy 2.12 MeV and a gamma-photon (155 keV, 15%) [180].

Tungsten-188 is loaded on the alumina generator as tungstic acid and it is eluted with saline. ^{188}W/^{188}Re generator, in chemical point of view, is almost the same as a ^{99}Mo/^{99m}Tc generator system, which is extensively studied. However, there is a major difference that originates from the availability of the mother radioisotopes (^{99}Mo and ^{188}W) as a carrier-free. The production process of ^{188}W results in a significantly carrier-added ^{188}W product (specific

activity <10 Ci/g of W, typically 4-8 Ci/g) [181] unlike ^{99}Mo which is generally produced from the fission of ^{235}U. Hence, the adsorption column of an ^{188}W/^{188}Re generator is considerably larger than that of a ^{99}Mo/^{99m}Tc generator at the same radioactivity. As a result, a large amount of elution is required to elute ^{188}Re at a reasonable quantity. In order to solve this problem concentration methods are utilized [182].

Uptake and Biokinetic Properties

A common use of ^{188}Re is in osseous metastases which stems from prostate and breast cancer. The ^{188}Re-radiopharmaceuticals used for that reason are ^{188}Re-hydroxyethylidene diphosphonate (^{188}Re-HEDP) and ^{188}Re dimercaptosuccinic acid (^{188}Re-DMSA). In most studies, a dose of 1,110 MBq (30 mCi) to 3,459 MBq (90 mCi) of ^{188}Re-HEDP is injected intravenously and whole body dynamic scans are obtained 1 to 6 days later. ^{188}Re-HEDP is mostly concentrated on bone metastases and its excretion rate through urine is 62% of the administered activity within the first 2 days [183]. The mean effective half-life was (15.9±3.5) h in bone metastases, (10.9±2.1) h in the bone marrow, (11.6±2.1) h in the whole body, (12.7±2.2) h in the kidneys and (7.7±3.4) h in the bladder [184]. The biodistribution of ^{188}Re-DMSA is similar to ^{99m}Tc analogue. ^{188}Re-DMSA shows selectivity for bone metastases and kidney, but uptake in normal bone is not significantly greater than in surrounding soft tissues [185].

Apart from the use of ^{188}Re in bone metastases, ^{188}Re labeled with 4 Hexadecyl-1, 2, 9, 9-tetramethyl-4, 7-Diaza-1,10-Decanethiol agent (^{188}Re-HDD) is also utilized for the treatment of hepatocellular carcinomas (HCC). The administration of the radiopharmaceutical is happening directly to the liver through a catheter which is inserted transfemorally and introduced into the proper hepatic artery. Regarding to its biokinetic properties, a fast blood clearance of the injected activity is observed with a calculated effective half-life of (7.6±2.2) h in blood. The predominant elimination of the activity was through urinary excretion with a mean renal clearance of (44.1±11.7) % of the injected activity within the 76 h post administration. Faecal elimination was negligible. The calculated whole-body effective half-life was (14.3±0.9) h [186].

Another compound, ^{188}Re-anti-CD20 is used for the treatment of non-Hodgkin's lymphoma. According to Garcia *et al*. [187] thirty minutes after administration the percentage of the injected activity (IA) in the liver, spleen and kidneys was (22.5±5.2) %, (4.5±2.1) % and (2.1±0.6) %, respectively. After 24 h, the liver, spleen and kidneys activity decreased to (5.5±0.4) %, (1.4±0.2) % and (0.52±0.10) % of IA, respectively.

Dosimetry

Many studies in dosimetry of [188]Re-HEDP have been conducted. Liepe *et al*. [184] gathered data from several clinical studies including 13 prostate cancer patients with skeletal involvement who were treated with 2.7-3.46 GBq [188]Re-HEDP. The effective half-life, residence time and radiation-absorbed dose values were calculated for the whole body, bone marrow, kidneys, bladder and 29 bone metastases. Calculations to determine the absorbed dose were performed using the MIRDOSE3.1. The following radiation-absorbed doses were calculated: (3.83±2.01) mGy/MBq for bone metastases, (0.61±0.21) mGy/MBq for the bone marrow, (0.07±0.02) mGy/MBq for the whole body, (0.71±0.22) mGy/MBq for the kidneys and (0.99±0.18) mGy/MBq for the bladder. In another study conducted from Savio *et al*. [188], 21 patients received 1.3 or 2.2 GBq, in single or multiple doses. Absorbed dose in bone marrow was estimated with MIRDOSE3. Single doses of low activity (1.3 GBq) were given to 12 patients. 9 patients received multiple doses. The dosimetric estimations for absorbed doses after single or multiple [188]Re-HEDP administration were: (2.3±0.9) cGy/37 MBq (1 mCi) bone marrow dose (BMD) and (71±37) cGy total body marrow dose (TBMD) for the first group of patients (received single dose) while (1.6±0.9) cGy/ 37 MBq (1 mCi) BMD and (83±55) cGy TBMD for the second group (received multiple doses). Maxon *et al*. [189] evaluate the [188]Re (Sn) HEDP as a radiopharmaceutical that localizes in skeletal metastases based on the prior experience of [186]Re-HEDP. *In vivo* and *in vitro* tests were conducted in patients and rats by using two models for calculating the radiation dose: the standard MIRD schema and an ICRP model. The calculated radiation doses in 5 patients with prostate cancer that were injected firstly with diagnostic administrations 177.6 MBq (4.8 mCi) − 185 MBq (5.0 mCi) were (5.2±1.2) cGy/37 MBq (or cGy/mCi) for kidneys, (3.6±1.1) cGy/37 MBq for bladder wall, (3.5±0.7) cGy/37 MBq for red marrow, (3.2±0.5) cGy/37 MBq for normal skeleton, (0.14±0.03) cGy/37 MBq for testes and (0.37±0.06) cGy/37 MBq for the whole body.

Apart from [188]Re-HEDP, [188]Re can be labeled with dimercaptosuccinic acid ([188]Re-DMSA) as a pain palliation agent since it is taken up in a variety of tumours and bone metastases. Blower *et al*. [185] investigated the biodistribution and the dosimetry of [188]Re-DMSA *in vitro* in mice and *in vivo* in 6 patients. Organ residence times were estimated from the scans and used to estimate radiation doses. The residence half-times for the source organs were (0.47±0.21) h in kidneys, (0.52±0.16) h in liver, (9.64±0.48) h in bladder contents and (10.44±1.50) h for the remainder of the body. Of the normal tissues, the kidneys received the highest radiation dose (0.5–1.3 mGy/MBq), the liver received (0.12±0.04) mGy/MBq and both red marrow and total body received (0.07±0.01) mGy/MBq.

Lambert *et al*. [186] studied the dosimetry of [188]Re-HDD-lipiodol for hepatocellural carcinoma (HCC) after the injection of 3.60GBq (range, 1.86– 4.14 GBq) [188]Re-HDD/lipiodol

to 11 patients. The absorbed doses to the various organs were calculated according to the MIRD formalism, using the MIRDOSE3.1 software. The absorbed dose to the liver tissue, the lungs, the kidneys and the thyroid was (4.5±1.9), (4.1±1.2), (0.9±0.7) and (0.3±0.1) Gy, respectively. Liepe *et al*. [190] studied the treatment of patients with unresectable colorectal liver metastases or hepatocellular cancer with [188]Re-microspheres. The administered activity was calculated to give a liver dose of 100 Gy. (13.6±4.7) GBq [188]Re-microspheres were administered selectively in the feeding artery of the tumour to 10 patients (3xHCC and 7xcolorectal liver metastases). The doses were calculated using the 'nodule module' option of MIRDOSE3.1 software. The absorbed dose to the tumour, normal liver (excluding the tumour) and bladder was (10.24±5.02) Gy/GBq (128±47 Gy), (3.94±2.52) Gy/GBq (50±33 Gy) and (0.27±0.20) Gy/GBq (2.4±1.9 Gy), respectively. Kumar *et al*. [191] evaluated dosimetry-guided transarterial radionuclide therapy (TART) with [188]Re-HDD-labeled iodized oil in inoperable hepatocellular carcinoma (HCC), in 93 patients after injecting 185 MBq of [188]Re-HDD iodized oil via the hepatic artery. The dosimetry of the target organs was based on MIRD schema and by adjusting the pertinent S factors for the difference in total body and organ masses between the patient and the anthropomorphic model. The absorbed dose to the tumour, normal liver and lungs was (1.491±0.519) cGy/MBq, (0.353±0.115) cGy/MBq, (0.037±0.019) cGy/MBq, respectively.

Garcia *et al*. [187] studied the biokinetics and dosimetry of [188]Re-anti-CD20 in 3 Patients with non-Hodgkin's lymphoma. Whole-body images were acquired at various times post administration, obtained from instant freeze-dried kit formulations with radiochemical purity >95%. ROIs were drawn around source organs in each time frame. The cpm of each ROI was converted to activity using the conjugate view counting method. The image sequence was used to extrapolate time-activity curves in each organ to calculate the total number of disintegrations (N) that occurred in the source regions. N data were the input for the OLINDA/EXM code to calculate internal radiation dose estimates. Dosimetric studies indicated that after administration of 4.87-8.72 GBq of [188]Re-anti-CD20, the absorbed dose to total body would be 0.75 Gy, which corresponds with the recommended dose for NHL therapies.

The use of [188]Re labeled with diethylene triamine penta-acetic acid (DTPA) agent has been also reported in bibliography in balloon angioplasty for the treatment of artherosclerotic coronary artery disease although it is in experimental state and the dosimetry is evaluated in animals or by Monte Carlo simulations [192, 193].

xiii) Astatium-211

Introduction

Astatium (or Astatine) -211 (^{211}At)was first characterized, in 1940 by Dale R. Corson (1914), Kenneth R. Mackenzie (1912-2002), and Emilio Segrè (1905-1989) (California), who synthesized the isotope ^{211}At by bombarding Bismuth with alpha particles [194, 195]. They have named the new element Astatine, from the Greek "astaton", which means restless, unstable because the element has no stable isotopes and the suffix -ine because that is usual for halogens [196]. ^{211}At is far too rare to have any uses. Intensive research in this field has already shown that it is promiscuous for targeted radiotherapy but ^{211}At is not yet a part of the clinical routine. The use of Astatine in medicine is still under investigation and the confirmation of its utility remains to be seen.

Production and Physical Characteristics

^{211}At (Z=85) is a radioactive halogen in solid phase, with the following physical characteristics: melting point 302 °C (576 °F), boiling point 337 °C (639 °F) [195]. It is an alpha emitter with a physical half-life of 7.2 h [197]. The production of ^{211}At, is accomplished by the ^{209}Bi (α, 2n) ^{211}At reaction in a cyclotron, namely by irradiating a ^{209}Bi target with 28-MeV α-particles. The ^{211}At then is isolated using a dry-distillation procedure [198].

Uptake and Biokinetic Properties

^{211}At is similar to the elements above it in Group 17 (VIIA) of the periodic table, especially Iodine. One property of Iodine is that it tends to collect in the thyroid gland. Astatine appears to behave like Iodine in the human body, accumulating in the thyroid, so it can be used as a radioactive tracer. Scientists speculate that, because of its high radioactivity, ^{211}At might be used to treat hyperthyroidism. An investigation of the efficacy of ^{211}At-Tellurium colloid for the treatment of experimental malignant as cites in mice reveals that this alpha-emitting radiocolloid can be curative without causing undue toxicity to normal tissue [199].

Another important use of ^{211}At in medicine is epitomized in labelling antibodies. Monoclonal antibodies (mAbs) labelled with α-emitting radionuclides such as ^{212}Bi, ^{213}Bi, and ^{212}Pb (which decays by β-emission to its α-emitting daughter, ^{212}Bi) are being evaluated for their potential applications in cancer therapy [200]. The fate of these radionuclides after cells are targeted with mAbs is important in terms of dosimetry and tumour detection. ^{211}At catabolism and release from cells were somewhat similar to that of ^{125}I whereas ^{205,6}Bi and ^{203}Pb showed prolonged cell retention similar to that of ^{111}In. These catabolism differences may be important in the selection of α-radionuclides for radioimmunotherapy.

Also, there are some researchers that create uptake ratios of N-Succinimidyl 3–[211At]Astato– 4–Guanidinomethylbezoate ([211At]SAGMB) to [131I]SGMIB in a series of experiments, using glioblastoma cells, showing a steadily increased uptake of [131I]SGMIB, especially in measurements 7 hours post injection [201-203]. The median cavity biological clearance half-time is 218 hours.

Meta-[211At] Astatobenzylguanidine ([211At] MABG) uptake in SK-N-SH neuroblastoma cells *in vitro* and tissue distribution in mice *in vivo* is very similar to MIBG [202-204].

Dosimetry

211At labelled to a monoclonal antibody has proven safe and effective in treating microscopic ovarian cancer in the abdominal cavity of mice, without significant toxicity, according to Andersson *et al*. [205]. Moreover, they demonstrated that the estimated absorbed dose to the peritoneum was (15.6±1.0) mGy/(MBq/L), to red bone marrow (0.14±0.04) mGy/(MBq/L), to the urinary bladder wall (0.77±0.19) mGy/(MBq/L), to the unblocked thyroid (24.7±11.1) mGy/(MBq/L) and to the blocked thyroid (1.4±1.6) mGy/(MBq/L), in a series of experiments, where 9 patients were infused with 211At-MX35 F(ab')$_2$ (22.4-101 MBq/L) in dialysis solution via the peritoneal catheter. 211At was labelled to MX35 F(ab')$_2$ using the reagent *N*-succinimidyl-3-(trimethylstannyl)-benzoate. Planar images, in addition to SPECT/CT, were acquired and also biological parameters were taken into account in order to lead to good dose estimation. Also, Monte Carlo simulation was undergone by the same scientific team to show respective results in a series of *in vitro* experiments, using cell lines [206].

In additional, there is some research, about the utility of 6-[[sup 211] At]-astato-MNDP. It is of a class of a high linear energy transfer endoradiotherapeutic drug, which selectively locates to an onco-APase isoenzyme expressed by certain epithelial and germ cell tumours. The therapeutic efficiency and acute toxicity of its endogenous [alpha]-particle emissions have been intensively studied in murine tumour models. [sup 211]At is produced by the [sup 207] Bi ([alpha], 2n)[sup 211]At cyclotron-based nuclear reaction. High specific therapeutic potential of 6-[[sup 211] At]-astato-MNDP was rapidly synthesized by *in vacuo* thermal heterogeneous isotopic exchange [207]. Significant therapeutic effects due to targeted [alpha]-particle emissions have been confirmed for the activity dose range of 10-750 kBq (0.00027-0.02000 mCi) without irreversible hematoxicity or stigmata of acute radiation damage in other critical normal tissues.

xiv) Bismuth-212

Introduction

Bismuth-212 (^{212}Bi) is a promising radioisotope that is intended to be used for melanoma radio-immunotherapy. Only preclinical studies on mice are currently published with promising results.

Production and Physical Characteristics

^{212}Bi is produced by chemistry generator from parent ^{224}Ra, according to the following decay chain (half-life time and type of decay are shown into the brackets): ^{224}Ra (3.6 d, a-emission)→^{220}Rn (56 sec, a-emission)^{216}Po →(0.15 sec, a-emission)→^{212}Pb (10.6 min, β$^-$-emission)→^{212}Bi. The radioactive ^{212}Bi decays to ^{208}Pb with physical half-life time of 60.55 min according to the following chains: ^{212}Bi (60.55 min, a-emission)→^{208}Tl (3 min, β$^-$-emission)→^{208}Pb and ^{212}Bi (60.55 min, β$^-$emission) → ^{212}Po (0.3 min, a-emission) → ^{208}Pb. The type, energy and emission ratio of each decay are displayed at Table 4.

Table **4***. ^{212}Bi decay chart

Type of decay	Energy (MeV)	Emission ratio (Bq·s)$^{-1}$
Alpha	6.207	0.3594
Beta (-)	2.254	0.6406
Beta (+,-), Alpha	11.208	0.014
Alpha	6.457	0.67
Beta (-)	2.504	0.33
Beta (-)	4.164	1

* McDevitt *et al.* [208]

The ^{212}Bi generator requires heavy shielding because the daughter nuclide ^{208}Tl emits high energy gamma photons at 2.6 MeV. Additionally, daughter ^{220}Rn appeared in the decay chain requires the ^{224}Ra cow be placed in either a gas-tight or trapped enclosure.

Uptake and Biokinetic Properties

[DOTA]-Re(Arg11)CCMSH has shown very promising results for future clinical development. Exhibited rapid tumour uptake and extended retention coupled with rapid whole body disappearance was observed at a preclinical study [209]. Also radionuclide ^{212}Bi offers

considerable promise in the treatment of microscopic ovarian carcinoma resistant to conventional treatment modalities [210].

Dosimetry

^{212}Bi is an α-emitter with high linear energy transfer. Recent preclinical research showed that it has high therapeutic results in melanoma tumours at mice. The melanoma targeting peptide, 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA)-Re(Arg^{11})CCMSH is radiolabeled with ^{212}Pb, parent of ^{212}Bi. Tumour absorbed dose estimation is 61 cGy/μCi, according to a study with mice suffering from melanoma tumour [210].

xv) Bismuth-213

Introduction

Bismuth-213 (^{213}Bi) is α- and β$^-$-emitter that is used for radio immunotherapy for leukemia. Leukemia therapy via ^{213}Bi has been a successful therapy for many patients during the last decade.

Production and Physical Characteristics

^{213}Bi is produced by chemistry generator from parent ^{225}Ac which is separated from ^{229}Th and its daughter isotope ^{225}Ra, according to the following decay chain (half-life time and type of decay are shown into the brackets): ^{225}Ac (10 d, α-emission)→^{221}Fr (4.8 min, α-emission) ^{217}At→(32 ms, α-emission)→^{213}Bi. The radioactive ^{213}Bi decays to ^{213}Po and ^{209}Tl with physical half-life time of 46.5 min according to the following chains: ^{213}Bi (46.5 min, a-emission) →^{209}Tl (2.2 min, β$^-$-emission) →^{209}Pb and ^{213}Bi (46.5 min, β$^-$-emission) →^{213}Po (3.72 μsec, a-emission) →^{209}Pb. The type, energy and emission ratio, of each decay, are displayed at table 5.

Table **5***. ^{232}Bi decay chart

Type of decay	Energy (MeV)	Emission ratio (Bq·s)$^{-1}$
Alpha	5.87	0.022
β$^-$	1.423	0.978
Alpha	8.536	1
β$^-$	3.99	1

* Bray *et al.* [211]

Uptake and Biokinetic Properties

HuM195 is a humanized, unconjugated, anti-CD33 monoclonal antibody that is radiolabeled to ^{213}Bi. ^{213}Bi-HuM195 is injected in patients and there is a significant uptake in liver, spleen and bone marrow [212]. Localization of the ^{213}Bi in the human body is expected to areas with leukemic involvement, including the bone marrow of the vertebrae and pelvis, the liver and the spleen. There is no significant uptake of the ^{213}Bi to the kidneys.

Dosimetry

Dosimetric calculations can be performed using planar scintigraphic images. According to a study by Sgouros et al. [213], the absorbed dose equivalent to liver and spleen ranged from 2.4 to 11.2 and 2.9 to 21.9 Sv, respectively. Bone marrow mean dose ranged from 6.6 to 12.2 Sv. The total-body dose ranged from 2.2×10^{-4} to 5.8×10^{-4} Gy. According to JG Jurcic *et al*. [214] study, mean absorbed dose was estimated at (9.8 ± 6.5) mSv/MBq for the bone marrow, (5.8 ± 1.6) mSv/MBq for the liver, (10.8 ± 5.4) mSv/MBq for the spleen and (2.6 ± 1.2) mSv/MBq for the blood. Mean absorbed doses ranged between 2.6-29.4 mSv/MBq for the bone marrow, 3.8-24.2 mSv/MBq for the spleen, 3.9-9.7 mSv/MBq for the liver and 1-5.1 mSv/MBq for the blood. Total dose equivalent to the liver, spleen and blood ranged between 2.4-23.5 Sv, 2.9-36.8 Sv and 1.1-11 Sv, respectively. The whole body absorbed dose was 0.0004 mSv/MBq.

xvi) Radium-223

Introduction

Radium-223 (^{223}Ra) is a radioisotope that was introduced for bone metastasis tumour cancer cells treatment in 2001. As with dissolved ^{89}SrCl2 (MetastronTM), Radium captions are incorporated within the bone matrix of metabolically active bone, probably by inclusion in the calcium hydroxyapatite crystals [215].

Production and Physical Characteristics

^{223}Ra is produced by a generator system using Actinium-227(^{227}Ac) as parent nuclide (half-life of 21.8 years) and has been developed by Atcher *et al.* [216]. ^{223}Ra has a half-life time of 11.43 days. The effective energy emitted per decay due to a-particles is 5.65 MeV [217].

Uptake and Biokinetic Properties

In a comparative study of ^{223}Ra and the beta-emitter ^{89}Sr it was shown that cationic ^{223}Ra and ^{89}Sr had almost the same bone uptake. Estimates of dose deposition in bone marrow

suggested an advantage of alpha-particle emitters for sparing bone marrow [218]. The use of the ^{223}Ra was extended to solid tumours and soft tissue metastases. One formula of liposomal doxorubicin (Caelyx™/Doxil™) is available for the treatment of cancer. Liposomal ^{223}Ra higher activity was observed in blood and soft tissues compared to cationic ^{223}Ra. Spleen had the highest uptake using liposomal ^{223}Ra while bone had the highest uptake using cationic ^{223}Ra [215].

Dosimetry

Cationic ^{223}Ra is used at radioimmunotherapy for prostate and breast cancer bone metastasis and a dose estimation study was performed according to the ICRP-67 model. These estimates indicated that for a 50 kBq per kg of bodyweight dosage, the bone surfaces would receive 13.05 Sv. The average bone-surface to red bone marrow dose ratio was estimated to be 10.3. The liver, the large intestines and the colon received equivalent doses estimated to 0.635, 0.367 and 0.254 Sv, respectively [219]. Silberstein *et al.* [220] estimated the tumour absorbed dose to be 8.1cGy/MBq for ^{89}Sr. This would then correspond to 243cGy/MBq and 12.15 Sv/MBq for ^{223}Ra in tumours [215].

III) DISCUSSION

This review article reports the most widely known radionuclides that have been utilized or even proposed for use in nuclear medicine therapy, both α-emitters and β-emitters. The physical characteristics, the uptake and biokinetics as well as the dosimetry of all these radioisotopes attached to specific agents for therapy have been extensively reported.

Each radiopharmaceutical is selected for therapy according to the radioisotope's physical characteristics as well as the agent compound chemical characteristics. Thus, there are radioisotopes that are used specifically in only one case of malignancy (e.g. bone cancer) while there are other which can be attached in more than one agent and, as a result, they can be used in more cases of malignancies (e.g. bone and liver).

The ultimate goal of nuclear medicine therapy is multiple; first, is the delivery of significant amount of radioactivity and, consequently, dose to the tumour. Secondly, there is an essential need for maximum decrease in the dose to the critical organs. Moreover, radioisotopes that can be also used for imaging purposes offer a great advantage in comparison to others. Thus, one of the most significant research' intentions is the production of radiopharmaceuticals that are directly administered to the malignancy as well as they are rapidly excreted from the body via urine in order to reduce the unnecessary exposure to as low as possible levels.

This article is referred to radiopharmaceuticals that have been used for the treatment of bone cancer, hepatic malignancies and thyroid pathological situations. More specifically ^{32}P, ^{89}Sr, ^{117m}Sn, ^{153}Sm, ^{166}Ho, ^{186}Re and ^{188}Re have been used for bone cancer therapy or bone pain palliation. Also, ^{90}Y, ^{166}Ho and ^{188}Re have been used for the treatment or palliation of hepatic malignancies.

For bone cancer therapy, ^{32}P and ^{89}Sr are the most old-known radioisotopes used. ^{32}P is no longer used as the toxicity levels to the normal tissues were significantly high. However, ^{89}Sr is currently used in many centres although its first use has been performed many years ago. From the rest, ^{117m}Sn are ^{153}Sm have been established in nuclear medicine therapy while ^{166}Ho, ^{186}Re and ^{188}Re are currently interfered in many studies and clinical trials which evaluate their potential use.

In the treatment of thyroid diseases, ^{131}I has been broadly established since several decades. Due to its synthesis, it has been proved the most successful therapeutic radiopharmaceutical for the thyroid as it concentrates on the gland and any metastasis. ^{211}At is a radionuclide under investigation for the treatment of thyroid diseases, as well.

For various lymphomas, the suitable radionuclides are ^{67}Cu (not currently used), ^{90}Y, and ^{188}Re while ^{177}Lu and ^{111}In are mostly used for neuroendocrine tumours. ^{212}Bi and ^{213}Bi have been utilized in the treatment of melanomas and leukemia, respectively.

The dosimetric methods for the quantification of the absorbed dose in critical organs and the tumour are evolved throughout time. In the dawn of the Nuclear Medicine, the absorbed dose in the patient was calculated through strict mathematical equations without any imaging data. Then, 2D dosimetry followed retrieving data from the SPECT images. 2D dosimetry was gradually replaced by 3D dosimetry which is the most predominant technique, nowadays. Many simulation programmes appeared and the need for the accurate estimation of the received dose is now imperative. Today, 3D techniques are highly developed and they estimate the dose with great accuracy compared to older techniques.

IV) CONCLUSION

Concluding, many radionuclides have been used in Nuclear Medicine therapy resulting in either complete treatment or pain palliation. The choice of the suitable radio-labelled chemical compound depends on parameters which characterize the tumour, the chemical properties of the agent and the physical properties of the radionuclide. Dosimetric methods are rapidly changed and much research is conducted to that direction. The most significant current trend which, additionally, needs further research is the wide establishment

and optimization of patient-specific dosimetry as this will contribute to even more precise dosimetric outcome.

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