INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Review Article

RADIOPHARMACEUTICALS FOR IMAGING OF HYPOXIC TUMORS: A REVIEW

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Article Received on: 07/09/12 Revised on: 12/10/12 Approved for publication: 11/11/12

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ABSTRACT

Radiopharmaceuticals are drugs containing a radionuclide and are used routinely in nuclear medicine for the diagnosis and therapy of various diseases. The mechanism of localization of the radiopharmaceutical in different organs provides the clue for designing of the agent meant for a specific organ or pathway. Various agent like F-18, Cu-64/67, I-123, and Tc-99m are used as imaging of hypoxic tumors. Of these, F-18-fluoromisonidazole and I-123-iodoazomycin arabinoside (IAZA) have been most widely studied clinically. Non-nitro-containing bioreductive complexes, such as the Cu-60/62/64 thiosemicarbazone ATSM and Tc-99m butylene amineoxime (BnAO or HL91), have also been evaluated. In particular, I-123-IAZA and Cu-60-ATSM have shown correlation with response to radiotherapy in preliminary clinical studies. However, more preclinical studies comparing imaging with validated invasive methods and clinical studies with outcome measures are required. Nuclear medicine is poised to play an important role in optimizing the therapy of patients with hypoxic tumors. The present review is concern with the various radiopharmaceuticals used for imaging of hypoxia.

Keywords: Hypoxia, Radiopharmaceuticals, Diagnostic agent, Nitroimidazole, SPECT, PET

INTRODUCTION

Hypoxia is a pathological condition in which the body as a whole (generalized hypoxia) or a region of the body (tissue hypoxia) is deprived of adequate oxygen supply. Hypoxia is a situation that arises in our body due to inadequate supply of Oxygen that compromises biologic functions. All mammalian tissues require a steady supply of oxygen to meet their metabolic demands. For metabolism to take place, surprisingly low level of oxygen (intracellular pressures of 3-5mm of oxygen) is sufficient[1]. The low intracellular concentration is the result of oxygen delivery by diffusion from the capillary to the intracellular environment. Perfusion of the tissue with blood flow beyond its demand (luxury perfusion) is a waste of cardiac work, while inadequate oxygen supplies limit the ability of intracellular metabolism to meet the cells energy needs. As oxygen supply is reduced, maximum output decreases, and systems are down regulated to maintain viability. For short period (seconds), cellular work can exceed the oxygen supply, but an oxygen debt occurs that must be repaid[2]. If the debt becomes too large, cellular integrity is threatened. As a result, normal tissue has an extensive network of mechanism to provide tight coupling between the tissues requirement for oxygen and the amount delivered to the tissue.

TYPES AND CAUSES OF HYPOXIA

1. Hypoxic hypoxia is a generalized hypoxia, an inadequate supply of oxygen to the body as a whole. The term "hypoxic hypoxia" specifies hypoxia caused by low partial pressure of oxygen in arterial blood. In the other causes of hypoxia that follow, the partial pressure of oxygen in arterial blood is normal.

Hypoxic hypoxia may be due to:

A) Low partial pressure of atmospheric oxygen such as found at high altitude or by replacement of oxygen in the breathing mix either accidentally as in the modified atmosphere of a sewer or intentionally as in the recreational use of nitrous oxide.

B) Low partial pressure of oxygen in the lungs when switching from inhaled anaesthesia to atmospheric air, due to the Fink effect, or diffusion hypoxia.

C) A decrease in oxygen saturation of the blood caused by sleep apnea or hypopnea

D) Inadequate pulmonary ventilation (e.g., in chronic obstructive pulmonary disease or respiratory arrest).

E) Shunts in the pulmonary circulation or a right-to-left shunt in the heart. Shunts can be caused by collapsed alveoli that are still perfused or a block in ventilation to an area of the lung. Whatever the mechanism, blood meant for the pulmonary system is not ventilated and so no gas exchange occurs (the ventilation/perfusion ratio is zero). Normal anatomical shunt occurs in everyone, because of the Thebesian vessels which empty into the left ventricle and the bronchial circulation which supplies the bronchi with oxygen.

2. Hypemic hypoxia in which arterial oxygen pressure is normal, but total oxygen content of the blood is reduced.

A)Hypoxia when the blood fails to deliver oxygen to target tissues.

B)Carbon monoxide poisoning which inhibits the ability of hemoglobin to release the oxygen bound to it.

C)Methaemoglobinaemia in which an abnormal version of hemoglobin accumulates in the blood

3. Histotoxic hypoxia in which quantity of oxygen reaching the cells is normal, but the cells are unable to effectively use the oxygen due to disabled oxidative phosphorylation enzymes. The effects of drinking alcoholic beverages is a common example.

4. Ischemic, or stagnant hypoxia in which there is a local restriction in the flow of otherwise well-oxygenated blood. The oxygen supplied to the region of the body is then insufficient for its needs. Examples are cerebral ischemia, ischemic heart disease and Intrauterine hypoxia, which is an unchallenged cause of perinatal death.

TREATMENT

1. To counter the effects of high-altitude diseases, the body must return arterial pO_2 toward normal. Acclimatization, the means by which the body adapts to higher altitudes, only partially restores pO_2 to standard levels. Hyperventilation, the body's most common response to high-altitude conditions, increases alveolar pO_2 by raising the depth and rate of breathing. However, while pO_2 does improve with

hyperventilation, it does not return to normal. Studies of miners and astronomers working at 3000 meters and above show improved alveolar pO_2 with full acclimatization, yet the pO_2 level remains equal to or even below the threshold for continuous oxygen therapy for patients with chronic obstructive pulmonary disease (COPD). In addition, there are complications involved with acclimatization. Polycythemia, in which the body increases the number of red blood cells in circulation, thickens the blood, raising the danger that the heart can't pump it.

2. In high-altitude conditions, only oxygen enrichment can counteract the effects of hypoxia. By increasing the concentration of oxygen in the air, the effects of lower barometric pressure are countered and the level of arterial pO_2 is restored toward normal capacity. A small amount of supplemental oxygen reduces the equivalent altitude in climate-controlled rooms. At 4000 m, raising the oxygen concentration level by 5 percent via an oxygen concentrator and an existing ventilation system provides an altitude equivalent of 3000 m, which is much more tolerable for the increasing number of low-landers who work in high altitude. In a study of astronomers working in Chile at 5050 m, oxygen concentrators increased the level of oxygen concentration by almost 30 percent (that is, from 21 percent to 27 percent). This resulted in increased worker productivity, less fatigue, and improved sleep.

3. Oxygen concentrators are uniquely suited for this purpose. They require little maintenance and electricity, provide a constant source of oxygen, and eliminate the expensive, and often dangerous, task of transporting oxygen cylinders to remote areas. Offices and housing already have climate-controlled rooms, in which temperature and humidity are kept at a constant level. Oxygen can be added to this system easily and relatively cheaply.

TUMOR HYPOXIA AND THEIR CAUSES

When certain cells in our body get mutated and start multiplying in an uncontrolled manner, they result in the development of the tumor. In tumors, the increased cell mass requires additional oxygen supplies to keep them alive. To meet this demand tumor produce a number of factors to promote the growth of new vessels into the lesion. However, often, the increased demand for oxygen outstrips the supply, rendering a portion of the tumor mass hypoxic[3]. Such regions or portions in tumors are called as hypoxic regions. Most tumors larger than 1 mm3 in volume contain regions of hypoxia as a result of the disordered blood vessel structure and increased diffusion distances.

Hypoxia in tumor develops in two ways. The first form is referred to as chronic hypoxia which results from long diffusion distances between the blood vessels in tumor. The second form known as acute hypoxia can develop as a result of spasm of aberrant tumor vasculature or compression of vessels caused by increased interstitial fluid pressure within the tumor. Biochemists and clinicians define hypoxia differently depending upon the aspect that they are studying. Biochemists defined it as oxygen limited electron transport; while physiologists and clinician define it as a state of reduce O2 availability. For most purposes and in lay man's terms hypoxia can be defined as a situation where the cells are devoid of oxygen[4].

RADIOPHARMACEUTICALS

Radiopharmaceuticals are drugs containing a radionuclide and are used routinely in nuclear medicine for the diagnosis and therapy of various diseases. Depending upon their medical applications radiopharmaceuticals are divided into two classes' viz. diagnostic radiopharmaceuticals and therapeutic radiopharmaceuticals. They are briefly discussed below.

Diagnostics Radiopharmaceuticals

Diagnostic radiopharmaceuticals are molecules which are tagged with a gamma ray emitting radioisotope. Such agents when administered into the body localize in certain organs or tissue, for which they are designed for, and the radiation emitted by the associated radionuclide could be detected from outside with the help of suitable instrument like gamma camera. The analysis of the resultant images obtained from the gamma camera could reveal useful information regarding the disease condition of the patient.

Therapeutic Radiopharmaceuticals

Therapeutic Radiopharmaceuticals are very similar much to the diagnostic radiopharmaceuticals but the only difference being the use of a therapeutic radionuclide instead of a diagnostic radionuclide. In this case the primary aim is not to get diagnostic information but to deliver therapeutic doses of ionizing radiations to specific diseased sites. Further discussion on therapeutic radiopharmaceuticals is beyond the scope of present work.

DESIGNING OF DIAGNOSTIC RADIOPHARMACEUTICALS

Structure of a radiopharmaceutical generally consists of four parts, though there are many exceptions. The four parts are the radionuclide, biomolecule, chelator and a Linker/Spacer. The chelater is connected with biomolecule with the help of a linker, whereas the chelater holds the radionuclide as shown in Fig.1. The general considerations when designing new diagnostic radiopharmaceuticals are its easy availability, low cost, optimum half-life of radionuclide, effective half-life of the radiopharmaceutical, emission of gamma photons of suitable energy (100-200 keV), negligible particulate emission i.e. decay by electron capture or isomeric transition, and high target to non-target ratio. These criteria are extremely stringent and therefore it is very difficult to get an ideal radiopharmaceutical for any given application and the best among the available is generally the agent of choice.

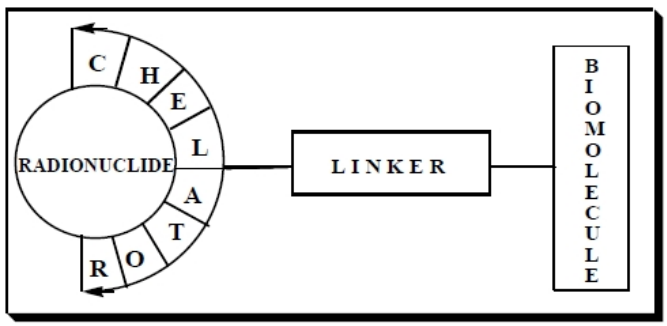

Figure 1: Schematic diagram of a radiopharmaceutical

Apart from these general considerations, an insight into the mechanism of localization of the radiopharmaceutical in different organs provides the clue for designing of the agent meant for a specific organ or pathway. The factors that need to be considered before, during and after the preparation of the radiopharmaceutical are specificity, compatibility, stoichiometry, charge and size of the molecule, solubility, stability, in vivo kinetic inertness, and protein binding capability[5].

Radionuclides for Diagnostic Radiopharmaceuticals

Radionuclides play a major role both in the imaging and radiotherapy of a disease. So choosing an ideal radionuclide

for the diagnostic and therapeutic radiopharmaceutical is an important factor. Diagnostic radionuclide imaging is commonly devised into two general modalities viz. Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Generally, typical imaging studies include dynamic or static imaging and in vivo function tests. Dynamic imaging provides clinicians with necessary data about biological turnover of radioisotopes in different body compartments and organs. Single-photon radionuclides emit gamma rays in the energy range of approximately 75 to 360 keV. Examples of these radionuclides are depicted in Table 1.

Radionuclide	Emission	Half-life	E-max(keV)	Production
^{131}I	γ (81.2%),beta	8.0 days	(γ),284,364,637	$^{131}Te(\beta),^{131}I$
^{111}In	γ	67.2 h	171,245	$^{111}Cd(n, p)$
^{123}I	γ	13.2 h	159	$^{121}Sn(\alpha,2n)$
^{99m}Tc	γ	6.0 h	140	$^{99}Mo/^{99m}Tc$-gen.
^{18}F	Positron	1.83 h	640	$^{18}O(p, n)$
^{11}C	Positron	20.4 min	960	$^{14}N(p, \alpha)$
^{13}N	Positron	9.96 min	1190	$^{16}O(p, \alpha)$
^{15}O	Positron	2.07 min	1720	$^{14}N(d, n)$

Radionuclides used in diagnostic radiopharmaceuticals

CURRENTLY USED RADIOPHARMACEUTICALS FOR IMAGING HYPOXIA

NON-INVASIVE MEASUREMENT OF TUMOR HYPOXIA WITH PET

1.[18F] Fluromisonidazole (FMISO)

This is one of the important and existing diagnostic radiopharmaceutical used for the detection of hypoxia in tumor. For diagnostic imaging studies 18F-Fluromisonidazole is injected by slow bolus intravenous injection at a dose of 3.7MBq/Kg (5.7 µg fluromisonidazole/Kg body weight). Imaging is started immediately and continued for 15 minutes. A 2 h post-injection image is also obtained. The short radiochemical half-life for 18F (112 min) requires that hypoxia marker retention be assayed before unbound marker is completely eliminated from tumor and normal tissue. A kinetic model is used to compute fractional hypoxic volumes (FHV) in the tumors[6]. In radiotherapy of head and neck cancer (HNC) and non-small cell lung cancer (NSCLC), hypoxia is known to be an important prognostic factor for long-term survival and local tumor control. The PET tracer (18)F-fluoromisonidazole (FMISO) allows noninvasive assessment of tumor hypoxia[7].Fluorine-18 fluoroerythronitroimidazole ([(18)F]FETNIM) is a nitroimidazole compound that is potentially useful as a hypoxia marker in positron emission tomography (PET) studies of oncological patients.

2.[^{18}F]FAZA ([^{18}F]fluoroazomycin-arabinofuranoside)

Sorger et al. compared the selective uptake of [^{18}F]FMISO and [^{18}F]FAZA in hypoxic cells in vitro and in a Walker 256 rat sarcoma model. The in vitro study showed that [^{18}F]FAZA is able to indicate reduced oxygen supply in the same order of magnitude of [^{18}F]FMISO. The in vivo study, however, indicated that [^{18}F]FMISO displayed a slightly higher standardized uptake value and tumour to muscle ratio compared to [^{18}F]FAZA though the elimination of the latter was much faster[8]. Two other studies also compared [^{18}F]FMISO and [^{18}F]FAZA in various tumour mice xenografts and reported superior biokinetics for [^{18}F]FAZA compared with [^{18}F]FMISO. In both studies [^{18}F]FAZA displayed higher tumour to background, tumour to muscle and tumour to blood ratios due to its more rapid clearance from blood and non-target tissues[9]

Souvatzoglou et al. evaluated the feasibility of [^{18}F]FAZA PET for the imaging of tumour hypoxia in 11 patients with head and neck cancer and concluded that PET imaging with [^{18}F]FAZA is feasible and that adequate image quality is achieved[10]. Another study, which included 18 patients with advanced squamous cell head and neck cancer, evaluated the role of [^{18}F]FAZA PET imaging to identify hypoxia in order to plan radiation treatment. It was concluded that radiation treatment planning and intensity-modulated radiotherapy based on [^{18}F]FAZA uptake measurements are feasible[11].

3.[^{18}F]FETA ([^{18}F]fluoroetanidazole)

In a study by Rasey et al., four cultured rodent cell lines were incubated with [^{18}F]FETA for various times under graded O_2 concentrations. The biodistributions of [^{18}F]FETA and [^{18}F]fluoromisonidazole (FMISO) at 2 and 4 h post-injection in C3H mice bearing KHTn tumours were also compared. [^{18}F]FMISO and [^{18}F]FETA demonstrated similar oxygen dependency of binding in cultured cells. However, differences in biodistribution suggested advantages of [^{18}F]FETA over [^{18}F]FMISO because [^{18}F]FETA appeared to be less metabolized in vivo than [^{18}F]FMISO[12]. In another study, the cellular transport and retention of [^{18}F]FETA were determined in vitro under air and nitrogen and the biodistribution and metabolism were determined in mice bearing several different xenografts. It was concluded that [^{18}F]FETA has suitable physicochemical properties and is stable to non-hypoxic degradation in vivo. It was also demonstrated that the tumour retention of the radiotracer is related to radiobiological hypoxia and pO_2 status as determined with polarographic needle oxygen electrodes[13].

4.[^{18}F]FETNIM ([^{18}F]fluoroerythronitroimidazole)

Pre-clinical data: Yang et al. reported on the synthesis and evaluation of [^{18}F]FETNIM. Their results indicated that at 4 h after injection, tumour to blood and tumour to muscle ratios in mammary tumour-bearing rats were significantly higher with [^{18}F]FETNIM than with [^{18}F]FMISO[14]. In a later study by Grönroos et al. where the pharmacokinetic properties and metabolite formation of [^{18}F]FETNIM were studied, [^{18}F]FETNIM showed low peripheral metabolism, little defluorination and possible metabolic trapping in hypoxic tumour tissue[15]. Clinical data: Most of the clinical studies with [^{18}F]FETNIM were performed in patients with head and neck cancer. A study investigating the accurate radiation dosimetry in 27 patients with head and neck cancer concluded that the effective dose of [^{18}F]FETNIM PET is well within the range of several related nuclear medicine procedures[16]. In another study, the radiotherapy response was assessed by hypoxia imaging with [^{18}F]FETNIM PET in 21 patients with head and neck cancer and high uptake of [^{18}F]FETNIM prior to radiation therapy was associated with a trend towards poor overall survival[17].

5.[^{18}F]EF5

In a study by Ziemer et al., the biodistribution of [^{18}F]EF5 was assessed using hepatoma and glioma rodent tumour models. [^{18}F]EF5 was rapidly and uniformly distributed to all tissues. This together with its high drug stability in vivo suggests that [^{18}F]EF5 is a promising agent for the non-invasive assessment of tumour hypoxia[18]. Differences in hypoxia between the different types of tumours could be detected with [^{18}F]EF5. Recently, the first human study with [^{18}F]EF5 was performed in 15 patients with squamous cell carcinoma of the head and neck (HNSCC) in which the time

course of [^{18}F]EF5 uptake after intravenous injection was evaluated to determine the most suitable PET protocol[19].

6.[^{18}F]EF3

Pre-clinical data: Mahy et al. studied the pharmacokinetics, biodistribution, metabolism and specificity for hypoxia of [^{18}F]EF3 in different tumour-bearing C3H mice breathing carbogen (5% CO_2, 95% O_2), 21% oxygen and 10% oxygen. They also compared [^{18}F]EF3 uptake and EF5 adducts detected by immunofluorescence in the same model. [^{18}F]EF3 uptake was inversely correlated with oxygen concentration, and a significant correlation was found between the [^{18}F]EF3 tumour to muscle ratio and the fluorescence intensity of EF5[20,21]. Pharmacokinetics, biodistribution and metabolism of [^{18}F]EF3 were assessed and compared with [^{18}F]FMISO uptake in rodent tumour models. It was concluded that both exhibited similar pharmacokinetics, biodistribution and metabolism and that [^{18}F]FMISO was able to detect tumour hypoxia to a similar extent as [^{18}F]EF3, although it seemed less specific than the latter tracer[22]. tumours. Clinical data: In a recent phase I study by Mahy et al., pharmacokinetics, biodistribution and metabolism of [^{18}F]EF3 were assessed in ten patients with head and neck squamous cell carcinoma. Administration of [^{18}F]EF3 seemed feasible and safe in head and neck cancer patients. Uptake and retention of the tracer was observed in the tumour, indicating the presence of hypoxia[23].

7.[^{18}F]EF1

Imaging with this marker was studied in two rat tumour types whereby the drug's biodistribution was assessed and optimized. [^{18}F]EF1 proved an excellent radiotracer for non-invasive imaging of tumour hypoxia[24].

8. [^{124}I]IAZA ([^{124}I]iodoazomycin arabinoside)

A IAZA has been frequently labelled with gamma rays-emitting isotopes of iodine ([^{123}I] and [^{125}I]), several studies report on the use of IAZA labelled with [^{124}I]. In a recent study by Reischl et al., the hypoxia imaging capacities of [^{124}I]IAZA, [^{18}F]FAZA and [^{18}F]FMISO were compared in female Balb/c nude mice bearing A431 tumours with a small animal PET scanner. [^{18}F]FAZA displayed significantly higher tumour to background ratio compared to [^{18}F]MISO and [^{124}I]IAZA. Although the tumour to background ratio for [^{124}I]IAZA increased with time, ratios were still lower than those for [^{18}F]FAZA at shorter time periods. The study demonstrated the superior biokinetics of [^{18}F]FAZA compared to [^{18}F]FMISO and [^{124}I]IAZA[25].

9.[^{18}F]FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose)

[^{18}F]FDG-PET is a non-invasive functional imaging method that is routinely used for cancer detection, staging and monitoring of response in several tumour types. Because the uptake of [^{18}F]FDG during FDG PET imaging relies largely on the expression of proteins that are under control of HIF-1, the degree of [^{18}F]FDG uptake by tumours might indirectly reflect the level of hypoxia. Reports trying to relate [^{18}F]FDG uptake with tumour hypoxia have, however, given inconsistent results. In vitro studies have suggested that FDG should be accumulated in hypoxic cancer cells compared to normoxic cancer cells because of changed metabolism . However, in vivo experiments (pre-clinical and clinical) have given conflicting results when showing a correlation between the uptake of [^{18}F]FDG and the existence of hypoxia in tumours . A recent review by Dierckx et al. addresses this subject matter[26].

10.Cu-ATSM

An ideal hypoxia imaging agent should have high membrane permeability for easy access to intracellular mitochondria and low redox potential to confer stability in normal tissue, but it should be able to be reduced by mitochondria with abnormally high electron concentrations in hypoxic cells. In this context, nitroimidazole residues are not considered to be essential. In this study, Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM), a 62Cu-bisthiosemicarbazone complex, with high membrane permeability and low redox potential, was evaluated as a possible hypoxia imaging agent, using electron spin resonance spectrometry and the Langendorff isolated perfused rat heart model as well as rat heart left anterior descending occlusion model.

Nonradioactive Cu-ATSM was incubated with rat mitochondria, after which reduction of Cu(II) to Cu(I) was measured with electron spin resonance. As a model of hypoxic mitochondria, rotenone (Complex I inhibitor)-treated mitochondria were used.

In this study, Cu-ATSM was reduced by hypoxic but not by normal mitochondria.

Thus, retention of 62Cu-ATSM was studied serially in perfused rat hearts under conditions of normoxia (95% O2 + 5% CO2), hypoxia (95% N2 + 5% CO2) and reoxygenation (95% O2 + 5% CO2). In normoxia and reoxygenation, 62Cu-ATSM injected as a single bolus showed low retention (23.77% and 22.80%, respectively) 15 min after injection, but retention was increased markedly under hypoxic conditions (81.10%). Also, in the in vivo left anterior descending occluded rat heart model, 62Cu-ATSM retention was inversely correlated with accumulation of 201Tl, a relative myocardial blood flow marker[27]

NON-INVASIVE MEASUREMENT OF TUMOR HYPOXIA WITH SPECT

1.[^{123}I]IAZA and [^{125}I]IAZA ([^{123}I]/ [^{125}I]iodoazomycin arabinoside)

This is one of the existing diagnostic radiopharmaceutical used for the detection of hypoxia in tumor . This is a molecule labeled with gamma-emitting isotopes (123I) which is detected by Single Photon Emission Computed Tomography (SPECT). In the 123I-SPECT studies, a series of radio iodinated azomycin nucleosides has been investigated, but 1-(5-iodo-5-deoxy-beta-D-arabinofuranosyl)-2-nitroimidazole (IAZA) has proven particularly useful. For non-invasive SPECT assay of tumor hypoxia, 123I-IAZA (176 to 370 MBq) is given by intravenous bolus injection. Imaging is started immediately assay the unbound marker before it completely eliminated from the tumor and normal tissue. Delayed (16 h - 24 h) imaging is then performed, allowing sufficient time for the clearance of unbound 123I-IAZA in plasma and extra cellular fluid, to observe the bound marker in the hypoxic cell[28].

Pre-clinical data: In one of the first studies with IAZA, its synthesis and labelling with [^{125}I] was described. Its elimination and biodistribution were also studied in vivo in EMT-6 tumours in BALB/c mice, and it was shown that IAZA undergoes hypoxia-dependent binding in EMT-6 cells in vitro[28]. Clinical data: The first clinical study assessing hypoxia with IAZA investigated the uptake of [^{123}I]IAZA in patients with advanced malignancies. Radiotracer avidity was observed in three of ten tumours, and it was concluded that the use of gamma emitter-labelled 2-nitroimidazoles as diagnostic radiopharmaceuticals is feasible and safe and that metabolic binding of [^{123}I]IAZA is observed in some, but not all tumours[30].

^{99m}Tc-LABELLED AGENT

1.BMS 181321

This was the first ^{99m}Tc-labelled 2-nitroimidazole to be widely studied for imaging[31]. A number of experimental studies have evaluated the use of BMS 181321 for the detection of ischaemic and hypoxic myocardium[32]. Ballinger et al. showed selective accumulation in hypoxic cells in vitro and in vivo but concluded that BMS 181321 was not optimal for tumour hypoxia imaging because of in vitro and in vivo instabilities and a high partition coefficient, resulting in slow clearance from the blood and high background levels in normal tissues[33].

2.BRU59-21

Pre-clinical data: BRU59-21, previously known as BMS 194796, is a second-generation analogue of BMS 181321 which shows greater stability in vitro and more rapid clearance from the circulation in vivo, resulting in higher tumour to blood and tumour to muscle ratios. It showed selective localization in tumour cells incubated under hypoxic conditions and following intravenous injection in animal models representative of poorly perfused tumours[34]. In a study by Zhang et al., BRU59-21 and HL91 were compared directly in the same in vitro systems. Both tracers proved suitable for hypoxia imaging[35].

Clinical data: Hoebers et al. assessed the safety and biodistribution of [^{99m}Tc]BRU59-21 in ten patients with head and neck cancer and correlated uptake in vivo with pimonidazole staining. In vivo evaluation of tumour hypoxia with [^{99m}Tc]BRU59-21 appeared to be safe and feasible, and uptake and retention of the marker seemed to be indicative of tumour hypoxia, as confirmed by pimonidazole staining[36].

3.[^{99m}Tc]HL-91

Pre-clinical data: Zhang et al. evaluated the efficacy of [^{99m}Tc]HL91 as a non-invasive marker of tumour hypoxia in vitro (Chinese hamster ovary cells) and in vivo (C3H mice bearing KHT-C tumours) and observed selective accumulation of [^{99m}Tc]HL91 in hypoxic cells and hypoxic tumours[37]. A similar study assessed the retention of [^{99m}Tc]HL91 in mice bearing three different tumours under control and enhanced oxygenation conditions and correlated these data with the oxygenation status as assessed by Eppendorf pO_2 histograph measurements. A very good correlation between [^{99m}Tc]HL91 retention and hypoxia, as measured by the Eppendorf histograph, was observed[38].

Clinical data: Clinical studies concerning the clinical evaluation of [^{99m}Tc]HL91 are limited. In a pilot study, Cook et al. compared [^{99m}Tc]HL91 uptake with [^{18}F]FDG PET imaging in ten patients with a variety of tumours and showed visible [^{99m}Tc]HL91 tumour uptake in all seven patients where the tumour could be clearly identified with [^{18}F]FDG PET[39].

Radio nuclides play a major role both in the imaging and radiotherapy of a disease.So choosing an ideal radionuclide for the diagnostic and therapeutic radiopharmaceutical is an important factor.Diagnostic radionuclide imaging is commonly devised into two general modalities viz. Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Generally, typical imaging studies include dynamic or static imaging and in vivo function tests. Dynamic imaging provides clinicians with necessary data about biological turnover of radioisotopes in different body compartments and organs. Single-photon radionuclides emit gamma rays in the energy range of approximately 75 to 360 keV.

CONCLUSION

There is a need to measure tumor hypoxia in assessing the aggressiveness of tumor and predicting the outcome of therapy. A number of invasive and noninvasive techniques have been exploited to measure tumor hypoxia, including polarographic needle electrodes, immunohistochemical staining, radionuclide imaging (positron emission tomography [PET] and single-photon emission computed tomography [SPECT]), magnetic resonance imaging (MRI), optical imaging (bioluminescence and fluorescence), and so on. It is well established that hypoxia is an important determinant of the overall response of the tumor to conventional therapy. The presence of hypoxia can result in an increase in tumor aggressiveness, failure of local control, and activation of transcription factors that support cell survival and migration. The ability to locate and quantify the extent of hypoxia within solid tumors by using noninvasive nuclear imaging would facilitate early diagnosis and help clinicians select the most appropriate treatment for each individual patient. Although SPECT is more commonly used than PET, and, in particular, ^{99m}Tc has a number of practical advantages that include ready availability at low cost, convenient half-life for hypoxia measurements and versatile chemistry as compared with ^{18}F, the superior spatial resolution and more accurate quantitation with PET makes the latter a better candidate for detection of tumoural hypoxia. Of all the PET tracers that are being evaluated as possible markers of tumour hypoxia, only three have been thoroughly evaluated in a clinical situation: [^{18}F]FMISO, [^{18}F]FDG and Cu-ATSM.

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Source of support: Nil, Conflict of interest: None Declared

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