Biomedicine & Pharmacotherapy 95 (2017) 469–476

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

The role of radionuclide probes for monitoring anti-tumor drugs efficacy: A brief review

Renata Salgado Fernandes[a,1], Carolina de Aguiar Ferreira[b,1], Daniel Cristian Ferreira Soares[c], Anna Margherita Maffione[d], Danyelle M. Townsend[e], Domenico Rubello[d,*], André Luís Branco de Barros[a,**]

[a] Laboratório de radioisótopos, Departamento de análises Clinicas, Universidade Federal de Minas Gerais (UFMG), Avenida Presidente Antônio Carlos, 6627, Belo Horizonte, Minas Gerais, Brazil
[b] Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI, 53705, USA
[c] Laboratório de Bioengenharia, Universidade Federal de Itajubá (UNIFEI), Rua Irmã Ivone Drumond, 200, Itabira, Minas Gerais, Brazil
[d] Department of Nuclear Medicine, Radiology, Medical Physics and Clinical Pathology, Santa Maria della Misericordia Hospital, Rovigo, Italy
[e] Department of Drug Discovery and Pharmaceutical Sciences, Medical University of South Carolina, USA

ARTICLE INFO

Keywords:
Anti-tumor efficacy
Therapeutic monitoring
Radiolabeled probes
Therapy response

ABSTRACT

Despite recent advances in the development of new therapeutic agents and diagnostic imaging modalities, cancer is still one of the main causes of death worldwide. A better understanding of the molecular signature of cancer has promoted the development of a new generation of anti-cancer drugs and diagnostic agents that specifically target molecular components such as genes, ligands, receptors and signaling pathways. However, intrinsic heterogeneity of tumors has hampered the overall success of target therapies even among patients with similar tumor types but unpredictable different responses to therapy. In this sense, post-treatment response monitoring becomes indispensable and nuclear medicine imaging modalities could provide the tools for an early indication of therapeutic efficacy. Herein, we briefly discuss the current role of PET and SPECT imaging in monitoring cancer therapy together with an update on the current radiolabeled probes that are currently investigated for tumor therapy response assessment.

1. Introduction

Cancer remains a major public health problem, accounting for 1 in each 6 deaths worldwide. The most common types of cancer are lung, colorectum, and prostate in men and lung, breast, and colorectum in women. In the United States alone, upwards of 600,920 cancer- related deaths are estimated for 2017 [1]. Over the last three decades, significant progress has been made in the anti-cancer field to develop new drugs with higher specificity, efficacy and reduced toxicity. In parallel, early diagnosis is recognized as essential for positive clinical outcomes and the field of nuclear medicine has developed probes for early detection and post-treatment monitoring. Consequently, active monitoring of the tumor response to treatment rises as an interesting tool that can be leveraged for personalized medicine [2]. Currently, the response to treatment is usually assessed by measuring the tumor size with computed tomography (CT) or magnetic resonance imaging (MRI), regardless of the fact that tumor shrinkage usually occur several weeks or months after treatment or it may not occur at all with certain therapies, even when patients show positive responses to treatment [3].

Better tools for monitoring response at earlier stages of treatment are urgently needed, the result of which could have several benefits such as reduced side effects as a result of unnecessary chemotherapy and the ability to spare medical costs [4]. Furthermore, detecting and predicting tumor response is essential for improving the ability to tailor individual therapies and rapidly evaluate novel anti-cancer strategies. Markers of response could include, e.g. changes in metabolism or receptor expression associated with tumor cell death or inhibition of proliferation, whereas predictors of response might include the expression of hormone receptors, which predict response to anti-hormonal treatment, or the presence of tumor hypoxia, which can affect the effectiveness of radiotherapy [2].

In this context, molecular imaging has become an indispensable tool to determine the efficiency of tumor therapy regimens. Single-photon emission computed tomography (SPECT) and Positron emission

* Corresponding author at: Nuclear Medicine, Radiology, Medical Physics and Clinical Pathology, Santa Maria della Misericordia Hospital, Via Tre Martiri 140, 45100 Rovigo, Italy.
** Corresponding author at: Faculty of Pharmacy, Federal University of Minas Gerais, Av. Antônio Carlos, 6627, 31270-901, Belo Horizonte, Minas Gerais, Brazil.
E-mail addresses: domenico.rubello@libero.it (D. Rubello), brancodebarros@yahoo.com.br (A.L.B. de Barros).
[1] These authors equally contributed to the writing of this article.

http://dx.doi.org/10.1016/j.biopha.2017.08.079
Received 2 August 2017; Received in revised form 17 August 2017; Accepted 20 August 2017

tomography (PET) imaging approaches are the main techniques utilized and possess advantages over other imaging modalities, including high sensitivity and specificity, precise quantification, and almost no limit to tissue penetration [5,6]. Additionally, in contrast to MRI or CT, nuclear medicine imaging techniques allows the possibility to investigate not only tissues' morphological characteristics but also tumor cells' function and the recording of substantial information on tumor metabolism [7]. The most commonly used isotopes for imaging purposes are technetium-99m, fluorine-18, cooper-64, gallium-68, and indium-111 [8], and their characteristics and clinical use are described in the following topics.

Molecular imaging offers a unique ability to monitor tumor characteristics in addition to size. Specifically, novel radiopharmaceuticals can be leveraged to identify and monitor tumor characteristics that can distinguish it from other tissues and from other stages of disease. More specifically, several tumor features, such as vascularization, hypoxia, glycolysis, overexpression of some receptors and tumor-cell proliferation might be used and explored as targets for radiolabeled molecules or nanoparticles.

In this review, we briefly discuss the current role of PET and SPECT imaging in monitoring cancer therapy, describe the main isotopes used by these techniques, and provide an update, focused on preclinical settings, on new imaging probes that holds the potential to determine and monitor tumor response to treatment.

2. Different radioisotopes for imaging

2.1. Gamma emitter isotopes

Technetium–99 m (^{99m}Tc) is one of the most abundantly used radionuclides in nuclear medicine due to its favorable properties that include a single 140 keV gamma photon emission and short half-life (6.02 h). In addition, this radioisotope is readily obtained in the form of pertechnetate directly from ^{99}Mo/^{99m}Tc generators on elution with physiologic saline [9]. The versatile chemistry of Technetium–99 m has been exploited to yield a plethora of different complexes used with success in nuclear medicine investigations through SPECT imaging. For example, imaging with ^{99m}Tc-(methylene) diphosphonate is the best method to detect skeletal metastases in cancer patients, with a lower radiation burden if compared to CT. In addition to initial staging patients, diphosphonate scintigraphy is widely employed to re-stage advance disease during or after treatment. ^{99m}Tc-labeled hydrazinonicotinyl-Tyr3-octreotide (EDDA/HYNIC-TOC) is commonly used for the management of neuroendocrine tumors (NET) [10–12]. Although the ^{68}Ga-DOTA-somatostatin analogue PET/CT is now the recommended standard method for imaging, staging and restaging most types of NET [13,14], the ^{99m}Tc-labeled platform represents a good alternative to Gallium-68 radiotracers where PET/CT or Gallium-68 generators are not available [15].

^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) was one of the first tracers used in breast cancer patients prior to PET imaging [16,17]. Novikov and co-workers (2015) investigated the potential role of ^{99m}Tc-MIBI in early stages to monitor and predict breast cancer response to neoadjuvant chemotherapy (NAC) [18]. Despite its high predictive value, at present this radiopharmaceutical is not routinely used in this clinical setting.

Several other radioisotopes have been used for SPECT imaging, both at clinical and pre-clinical settings such as ^{67}Ga, ^{186}Re, ^{201}TI, ^{131}I,^{123}I and ^{111}In. For example, ^{123}I and ^{131}I are currently used in the diagnosis and treatment of thyroid cancer while ^{111}In, is commonly used for labeling Octreoscan, a somatostatin analogue available in the market for scintigraphic localization of primary and metastatic NET overexpressing somatostatin receptors [19]. In addition, some isotopes may have non-oncologic indications, such as ^{67}Ga [20] that is used to investigate chronic granulomatous diseases as sarcoidosis and ^{201}TI, used as a perfusion agent to study coronary artery disease evaluation [21].

2.2. Positron emitter isotopes

The radioisotope Fluorine-18 (^{18}F) has gained considerable attention due to its nuclear and physical characteristics suitable for PET imaging, including a half-life of 109.7 min and positron emission with low energy (max. 0.635 MeV) and ratio around 97%. Fluorine has favorable chemistry due to its high electronegativity, ability to establish stable bonds with carbon atoms and to act, in many cases, as bioisostere with hydrogen and oxygen [22,23]. The glucose analogue 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) is a clinically well-established PET tracer used in diagnosis and management of various malignancies. Independent studies have demonstrated that a reduction in FDG uptake is noted in patients that respond relative to those who do not [24–26]. In addition, increased FDG uptake after treatment is often associated with a high risk for early recurrence and poor prognosis [2]. Janssen and coworkers [27] evaluated metabolic responses of rectal cancer patients with PET/CT scans, in which FDG uptake was significant reduced in tumor areas only 1 week after chemoradiotherapy, demonstrating the feasibility of a very early response assessment.

Another fluorinated PET radiotracer, 3′-deoxy-3′-fluorothymidine (^{18}F-FLT), is a nucleoside analogue that, after being taken up by the cell, is phosphorylated by thymidine kinase 1 into ^{18}F FLT monophosphate, causing intracellular sequestration of radioactivity. Thymidine kinase 1 is a principal enzyme in the salvage pathway of DNA synthesis. Therefore, FLT allows a non-invasive assessment of tumor proliferation as well as early response to chemotherapy by PET [28]. The role for FLT PET imaging in oncology is in the identification of resistant tumor subvolumes and the possibility to monitor early treatment response rather than in tumor staging [2]. ^{18}F FLT has been used to monitor response to treatment in several types of cancer, such as glioblastoma [29], lung [30] and breast cancer [31]. Despite promising studies, FLT does not play a significant role in clinical setting. This is in part due to its relatively lower uptake in comparison with FDG, affecting the detection and its sensitivity. However, FLT can have advantages over FDG regarding monitoring response to treatment such as better imaging of brain tumors, increased sensitivity to therapies that have higher effect on cell division than on glucose uptake (cytostatic therapies) and possibly lower uptake due to inflammatory response [32]. These features implicate the need to modify analogues with more favorable uptake.

Copper-64 (^{64}Cu) radioisotopes are also important medical radionuclides due to its physical characteristics such as half-life of 12.7 h, beta negative decay with energy of 190.2 KeV as well as positron and gamma emission with $E_{average}$ = 280.2 KeV; E_{max} = 660 KeV and 1346 KeV [33]. These characteristics enable this radionuclide to be used both in PET imaging and for radionuclide radiotherapy. Cupper radioisotopes can be found in two different oxidation states, Cu^{+1} and Cu^{+2}, that permits its conjugation into different molecules, constituting radiopharmaceuticals for PET imaging of cancer. The well-established coordination chemistry of copper radioisotopes allows for its reaction with a wide variety of chelator agents that can be further linked to antibodies, peptides, proteins and nanostructured nanomaterials [34].

Fujibayashi et al. [35] developed a neutral lipophilic complex diacetyl-2,3-bisN4-methyl-3-thisemicarbazone (^{64}Cu-ATSM) that have interesting hypoxia-selective properties. This is important clinically as it is well known that hypoxia is correlated to tumor aggressiveness, resistance to radiotherapy and chemotherapy, increased risk of invasion and metastasis and poor prognosis [28]. Thus the ability to quantifying the extent of hypoxic tissue within a mass may be important to develop a therapeutic platform with greater success rates. A similar compound, ^{64}Cu-diacetyl-bis ethylthiosemicarbazone (^{64}Cu-ATSE), has a wider tissue-oxygenation level specificity than ^{64}Cu-ATSM and, in clinical trials, have provided images of tumor hypoxia that improved the clinical outcome of patients submitted to external beam radiotherapy [36].

Another PET tracer that is available for imaging regions of hypoxia, is the 2-nitroimidazole derrivative [^{18}F]-fluoromisonidazole (^{18}F-FMISO). In hypoxic cells FMISO maintains the extra electron because of