Physica Medica 43 (2017) 1–5

Contents lists available at ScienceDirect

Physica Medica

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

Technical note

A three-time-point method for assessing kinetic parameters of ^{64}Cu-labeled Ramucirumab trapping in VEGFR-2 positive lung tumors

Eric Laffon*, Roger Marthan

CHU de Bordeaux, Services de Médecine Nucléaire, Exploration Fonctionnelle Respiratoire, F-33604 Pessac, France
Univ Bordeaux, Centre de Recherche Cardio-Thoracique, F-33076 Bordeaux, France
INSERM U 1045, Centre de Recherche Cardio-Thoracique, F-33076 Bordeaux, France

ARTICLE INFO

Keywords:
Kinetic model
^{64}Cu-labeled PET tracer
VEGFR
Irreversible/reversible trapping

ABSTRACT

Objective: To describe a three-time-point method for estimating kinetic parameters involved in ^{64}Cu-labeled Ramucirumab (^{64}Cu-NOTA-RamAb) trapping of VEGFR-2 positive lung tumors.
Materials and methods: Positron emission tomography (microPET) data of tumor-bearing mice for ^{64}Cu-NOTA-RamAb trapping in VEGFR-2 positive HCC4006 tumor were used, involving tissue activity measurements acquired at 3, 24 and 48 h post-injection, without and with administration of RamAb blocking dose. A kinetic model provided an analytical formula describing the tissue time-activity-curve, involving ^{64}Cu-NOTA-RamAb uptake (Ki), release rate constant (k_R) and fraction of free tracer in blood and interstitial volume (F).
Results: Fitting analytical formula outcomes on mean microPET data yielded values of the kinetic parameters: Ki = 0.0314/0.0123 gram of blood per hour per gram of tissue, k_R = 0.0387/0.0313 h^{-1} and F = 0.2075/0.2007 gram of blood per gram of tissue, without/with RamAb blocking dose, respectively (R = 0.99999 for the graph displaying microPET versus theoretical data; $P < .01$).
Conclusions: Three independent kinetic parameters (Ki, k_R and F) can be assessed from three data points acquired at early, mid and late imaging, i.e., at 3, 24 and 48 h post-injection, for further characterization of ^{64}Cu-NOTA-RamAb trapping in VEGFR-2 positive lung tumors.

1. Introduction

Positron emission tomography (PET) imaging with 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) is a commonly utilized measurement tool for assessing changes in glucose metabolism level of malignant tissues owing to treatment [1]. However, ^{18}F-FDG PET imaging may not be appropriate to precisely evaluate response to specific cancer treatments such as those targeting vascular endothelial growth factor receptor-2 (VEGFR-2). VEGFR-2 is involved in endothelial cell proliferation and its overexpression is associated with poor prognosis in several tumors [2,3]. Novel PET imaging agents are thus required and Luo et al. have recently reported quantitative data about the characterization of an antibody-based imaging agent, namely ^{64}Cu-labeled Ramucirumab (^{64}Cu-NOTA-RamAb), which was designed for PET imaging of VEGFR-2 expression in vivo [4]. In nude mice bearing xenograft tumors, PET imaging with ^{64}Cu-NOTA-RamAb revealed specific and prominent uptake in VEGFR-2 positive HCC4006 lung tumors, whereas blocking experiments revealed significantly lower uptake. These findings were obtained from three-time-point tissue activity measurements, that is, at early (3 h), mid (24 h) and late imaging (48 h post-injection (p.i.)). However, comprehensive characterization of ^{64}Cu-NOTA-RamAb trapping in VEGFR-2 positive lung tumors, including possible trapping reversibility, might be of interest in particular for assessing response to VEGFR-2-targeted therapies, thus emphasizing the need for a further kinetic model analysis (KMA).

From experimental data of ^{64}Cu-NOTA-RamAb trapping acquired at early, mid and late imaging, in nude mice bearing VEGFR-2 positive lung tumors by Luo et al., we suggest that three independent kinetic parameters can be assessed, namely uptake rate constant (Ki), release rate constant (k_R), and fraction of free tracer in blood and interstitial volume (F) [4]. For each of the Luo et al.'s experiment in VEGFR-2 positive HCC4006 lung tumor, we adapted a previously published two-compartment KMA involving Ki, k_R and F, for fitting on microPET data of tracer uptake at 3, 24 and 48 h p.i. [4–6]. Additionally, for comparison, the same method was applied to further results obtained by Luo et al. in VEGFR-2 negative A549 lung tumors.

2. Materials and methods

First, an analytical input function (IF) for ^{64}Cu-NOTA-RamAb in

* Corresponding author at: Service de Médecine Nucléaire, Hôpital du Haut-Lévêque, Avenue de Magellan, 33604 Pessac, France.
E-mail address: elaffon@u-bordeaux.fr (E. Laffon).

http://dx.doi.org/10.1016/j.ejmp.2017.10.001
Received 10 August 2017; Received in revised form 29 September 2017; Accepted 2 October 2017

mice was obtained from mean blood radioactivity data published by Luo et al. without and with receptor RamAb blocking dose, respectively [4]. Then, a KMA-based analytical formula was derived describing the tissue time-activity-curve (TAC) in tumors, involving Ki, k_R, and F.

2.1. Analytical IF for ^{64}Cu-NOTA-RamAb in mouse

Mean blood radioactivity data obtained by Luo et al. (from n = 4 mice) in VEGFR-2 positive HCC4006 tumors at 3, 24, and 48 h p.i., i.e. $A_b(t)$ = 13.0, 10.9 and 9.8%ID/g (percentage of injected activity per gram of tissue: g^{-1}), respectively, were used [4]. (These values were the same as those of VEGFR-2 negative A549 lung tumors.) Decay correction was removed, that is, Luo's data were multiplied by exp $(-\lambda t)$ where "λ" is the ^{64}Cu physical decay constant ($\lambda = \ln 2/12.7\,h^{-1}$). Then, according to Thurber et al., the data were fitted with a decreasing mono-exponential function, with a time constant α (uncorrected for physical decay; expressed in h^{-1}, coherently with λ unit) [7]:

$$A_b(t) = A_b(t=0) \times e^{-\alpha \times t} \quad (1)$$

In Eq. (1), $A_b(t) = C_b(t) \times 100/ID$ (percentage of injected activity per gram of blood: g^{-1}), ID is the injected activity (MBq), and $C_b(t)$ is the blood radioactivity concentration at time t (activity per gram of blood: $MBq.g^{-1}$). At t = 0, assuming instant homogenization of the tracer after injection and blood density of 1, $C_b(t = 0) = ID/iDV$ where iDV is the initial (apparent) distribution volume (mL), leading to $iDV = 100/A_b(t = 0)$.

Similarly, mean blood radioactivity data obtained by Luo et al. (from n = 3 mice) in VEGFR-2 positive HCC4006 tumors at 3, 24, and 48 h p.i. after administration of a RamAb blocking dose (50 mg/kg of RamAb), i.e. $A_b(t)$ = 12.2, 9.1 and 7.8%ID/g, were used to obtain a mono-exponential IF.

2.2. Analytical formula for ^{64}Cu-NOTA-RamAb trapping

For each of Luo et al.'s experiments, i.e. in VEGFR-2 positive HCC4006 tumors without/with receptor blocking and in VEGFR-2 negative A549 tumors, an analytical formula describing the ^{64}Cu-NOTA-RamAb tissue TAC (uncorrected for physical decay) was used. It was derived from a previously published KMA, including the corresponding IF, and may be considered as a 1-tissue compartmental model extended to a 2-tissue compartmental model [6,8]:

$$A_T(t) = [Ki \times A_b(t=0) \times (e^{-\alpha \times t} - e^{(-\lambda + k_R) \times t})/(\lambda + k_R - \alpha)] + F \times A_b(t) \quad (2)$$

The first term in the right hand side of Eq. (2) (included in brackets) is related to trapped ^{64}Cu-NOTA-RamAb. The second term in the right hand side of Eq. (2) is related to free tracer in blood and interstitial volume. Actually, Eq. (2) expressing tissue TAC has a common origin with generalized Patlak's equation that involves a release rate constant k_R [8,9]. However, unlike the latter, an integral has been analytically solved in Eq. (2) by using a mono-exponential IF (uncorrected for physical decay). Coherently with α and λ unit, and since radioactivity data by Luo et al. were expressed in percentage of injected activity per gram tissue (%ID/g), Ki, k_R and F were expressed in $g.h^{-1}.g^{-1}$ (gram of blood per hour per gram of tissue), h^{-1} and $g.g^{-1}$ (gram of blood per gram of tissue), respectively.

2.3. Estimating Ki, k_R and F

For each of Luo et al.'s experiments, Eq. (2) yielded a system of three independent equations, each equation involving the same (experiment-specific) mean IF, a specific p.i. time delay "t" (, i.e. either 3, 24, or 48 h), and the three unknown parameters (, i.e. Ki, k_R and F). As a consequence of this equation system, when $A_T(t)$ is known at each specific p.i. time delay "t" from mean microPET data, one specific value for each parameter can solve the three-equation system. Since Eq. (2) involves exponential functions, we obtained the specific values of the three kinetic parameters by using nonlinear regression (GraphPad Prism software, version 5.00).

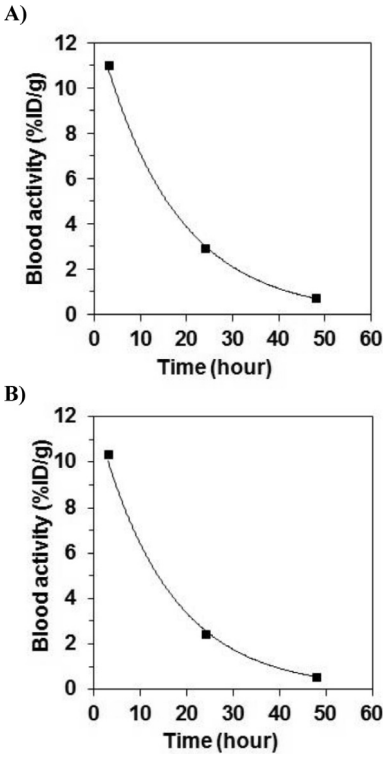

Fig. 1. Decreasing mono-exponential fitting of the input functions. Without (A) and with (B) receptor blocking: $A_b(t) = 13.039 \times \exp(-0.0610 \times t)$ (R = 0.99985; P < .02) and $A_b(t) = 12.195 \times \exp(-0.0640 \times t)$ (R = 0.99945; P < .05), respectively.

Estimating the magnitude of the measurement uncertainty (MU) of the kinetic parameters was made by using experimental data of VEGFR-2 positive HCC4006 tumors without receptor blocking. In accordance with the coefficient of variation of 10% recently reported for the standard uptake value (SUV) in ^{18}F-FDG PET imaging by Lodge, we assumed ± 10% relative MU for $A_T(t)$ at each p.i. time delay "t". As a result, three upper and three lower values of $A_T(t)$ yielded two further equation systems, respectively [10]. Solving each equation system provided further specific values for Ki, k_R, and F that were used to plot upper and lower (± 10%-MU) TACs on both sides of the mean one, respectively. For each kinetic parameter, comparison of the upper and lower values with the mean one led to an estimation of its MU.

3. Results

Fig. 1 shows the fitting of the two experimental mean IFs with decreasing mono-exponential functions for the VEGFR-2 positive HCC4006 tumors without and with receptor blocking, respectively. An estimate of the initial distribution volume may be obtained from the amplitude of the IF fitting: iDV = 7.67 mL (=100/13.039) and 8.20 mL (=100/12.195), respectively.

For each of Luo et al.'s experiments, the nonlinear correlation coefficient of the graph displaying mean microPET data versus theoretical data was found to be R = 0.99999 (P < .01). Values for the ^{64}Cu-NOTA-RamAb uptake and release rate constant and for the fraction of the free tracer in blood and interstitial volume, which solved the three-equation system in each experiment, were found to be: Ki = 0.0314/0.0123/0.0147 $g.h^{-1}.g^{-1}$, k_R = 0.0387/0.0313/0.0528 h^{-1} and F = 0.2075/0.2007/0.1625 $g.g^{-1}$, for VEGFR-2 positive HCC4006 tumors without/with receptor blocking and VEGFR-2 negative A549 tumors, respectively.