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COMMENTARY

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An abbreviated therapy-dosimetric equation for the companion diagnostic/therapeutic [$^{64/67}$Cu]Cu-SARTATE

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Abstract

In a preclinical model of neuroblastoma, Dearling et al. recently demonstrated the potential interest for a theranostic approach of [^{64}/^{67}Cu]Cu-SARTATE for the detection and treatment of SSTR2-positive neuroblastoma lesions in pediatric patients whose widespread metastases survive initial therapy as minimal residual disease (MRD). MRD may be detected by [^{64}Cu]Cu-SARTATE and subsequently treated by [^{67}Cu]Cu-SARTATE. Since therapeutic dosimetry estimation of the latter agent from the uptake of the former one in the initial diagnostic scan was not addressed, the present theoretical commentary proposes the derivation of an abbreviated therapy-dosimetric equation for the companion diagnostic/therapeutic [^{64}/^{67}Cu]Cu-SARTATE that might be of interest for future clinical theranostic practice.

Keywords: Theranostics, SARTATE, Dosimetry, Cumulated activity, Neuroblastoma

Background

Companion diagnostic/therapeutic radiopharmaceuticals (D-RP/T-RP) are the basis of the theranostic strategy that uses a molecule designed for a specific target, which is labeled with a suitable pair of radionuclides [1, 2]. The strategy consists in a first diagnostic PET-imaging scan with D-RP that selects patients who can subsequently benefit from a therapy with T-RP. It therefore appears instrumental to predict cumulated activity ($\tilde{A}_C$), and, hence, delivered radiation-dose of T-RP in tumors, from D-RP uptake in the initial diagnostic scan. In this connection, a model was previously proposed for comparing kinetic parameters and $\tilde{A}_C$ of the companion ^{64}Cu/^{177}Lu-cetuximab [2].

Recently, the [^{64}Cu]Cu-SARTATE biodistribution was assessed by Dearling et al. in a preclinical intrahepatic model of neuroblastoma (NB) metastatic disease, representing minimal residual disease (MRD), along with potential therapeutic effect of [^{67}Cu]Cu-SARTATE [1]. Unlike the companion ^{64}Cu/^{177}Lu-cetuximab, whose input function (IF, i.e., RP-blood time-activity-curve) was different for diagnosis/therapy (time constant of mono-exponentially decaying IF of 0.0830 h^{-1} and 0.0224 h^{-1}, uncorrected for physical decay, respectively), the companion [^{64}/^{67}Cu]Cu-SARTATE provides the opportunity of using a "true" theranostic pair of radionuclides, resulting in identical D-RP/T-RP uptake features [1, 2].

The present theoretical commentary aims at deriving an abbreviated equation of therapeutic $\tilde{A}_C$ with [^{67}Cu]Cu-SARTATE, from [^{64}Cu]Cu-SARTATE uptake assessed in a single initial diagnostic scan. In the pre-clinical framework of Dearling et al., this equation was refined by using the common mouse IF of [$^{64/67}$Cu]Cu-SARTATE and the physical-decay-rate constant of the $^{64/67}$Cu radionuclides [1].

Methods

Derivation

Assuming irreversible trapping, when PET imaging is acquired at peak time of decay-uncorrected trapped-tracer-activity concentration, it has been shown that [3]:

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$$\mathrm{SUV_{Tumor}}(t_{\text{peak - uncorr}})/\mathrm{SUV_{Blood}}(t_{\text{peak - uncorr}}) = K_i/\lambda + F \quad (1)$$

where $\mathrm{SUV_{Tumor}}$ and $\mathrm{SUV_{Blood}}$ (g mL^{-1}) are the mean standard-uptake-value in tumor and blood, respectively, K_i (mL time^{-1} mL^{-1}) is the tracer uptake-rate constant in tumor, λ (time^{-1}) is the tracer physical-decay-rate constant and F (mL mL^{-1}) is the fraction of free tracer in blood and interstitial volume (i.e., Patlak-plot y-intercept).

Furthermore, the total number of disintegrations $\tilde{A}_C$ (i.e., cumulated activity; Bq s) occurring in tissue volume V (mL) after tracer injection can be estimated as [2, 4]:

$$\tilde{A}_C = V \times [\tilde{A}\_\mathrm{IF}] \times [(K_i/\lambda) + F] \quad (2)$$

where $[\tilde{A}\_\mathrm{IF}]$ (Bq s mL^{-1}) is the area under curve of the tracer decay-uncorrected IF.

Applying Eq. 1 to D-RP leads to:

$$K_{i-T} = k \times \lambda_D \times [\mathrm{SUV_{Tumor\ -\ }}_D(t_{\text{peak - uncorr}})/\mathrm{SUV_{Blood\text{-}}}_D(t_{\text{peak - uncorr}}) - F_D] \quad (3)$$

where $k = K_{i\text{-}T}/K_{i\text{-}D}$, λ_D is the physical-decay-rate constant of [^{64}Cu]Cu-SARTATE and $\mathrm{F_D}$ is its free fraction in blood and interstitial volume.

Incorporating Eq. 3 into Eq. 2 applied to T-RP yields the general equation of its cumulated activity:

$$\tilde{A}_{C-T} = V \times \left[\tilde{A}\_\mathrm{IF}_{-T}\right] \times [k \times (\lambda_D/\lambda_T) \times [\mathrm{SUR}_D(t_{\text{peak - uncorr}}) - F_D] + F_T] \quad (4)$$

where λ_T is the physical-decay-rate constant of [^{67}Cu]Cu-SARTATE, $\mathrm{F_T}$ is its free fraction in blood and interstitial volume, and $\mathrm{SUR_D}(t_{\text{peak-uncorr}})$ is the tumor-to-blood SUV ratio (no unit) assessed at peak time of decay-uncorrected activity concentration of trapped D-RP [5].

Input function of [$^{64/67}$Cu]Cu-SARTATE and peak time

Mean blood-clearance data provided by Dearling et al. were used to fit the common IF of [$^{64/67}$Cu]Cu-SARTATE, after removing decay correction (GraphPad Prism 6 software) [1]: $\mathrm{IF}(t) = Y_0 \times \exp(-\alpha \times t)$ with $Y_0 = 4.11939$ %IA/g (IA: injected activity in Bq) and $\alpha = 0.18934$ h^{-1} (n = 4; $R = 0.999$; $P < 0.01$; 95%-CI of 4.08542–4.15335 and of 0.18579–0.19289, respectively). As a result, $[\tilde{A}\_\mathrm{IF}_{\text{-}T}]$ involving [^{67}Cu]Cu-SARTATE was $783 \times \mathrm{IA}$ mL^{-1} ($= [Y_0 \times \mathrm{IA} \times 3600]/[100 \times \alpha]$), assuming tissue density of 1 g mL^{-1}.

Peak time of decay-uncorrected activity concentration of trapped [^{64}Cu]Cu-SARTATE was assessed from an analytical solution of the nonlinear Patlak's equation, involving the above-reported mono-exponentially decaying IF [6]:

$$C_{\text{Trapped - }D}(t) = Y_0 \times K_{i-D} \times [\exp(-\alpha \times t) - \exp(-\lambda_D \times t)]/[\lambda_D - \alpha] \quad (5)$$

Peak time could thus be graphically determined, and, when solving Eq. 5 for $\mathrm{dC_{Trapped\text{-}}}_D(t)/dt = 0$, could be alternatively computed as $t_{\text{peak-uncorr}} = \mathrm{Log}(\alpha/\lambda_D)/(\alpha - \lambda_D)$. Furthermore, $\mathrm{SUR_D}(t_{\text{peak-uncorr}})$ ($= \mathrm{SUV_{Tumor\text{-}D}}(t_{\text{peak-uncorr}})/\mathrm{SUV_{Blood\text{-}D}}(t_{\text{peak-uncorr}})$) in Eq. 4 was obtained by adding the term "$\mathrm{F_D} \times \mathrm{IF}(t_{\text{peak-uncorr}})$" to Eq. 5 right-hand side and by dividing the whole by $\mathrm{IF}(t_{\text{peak-uncorr}})$, since the tumor-to-blood SUV ratio equals the tumor-to-blood activity–concentration ratio [6].

Results

Figure 1 shows the decay-uncorrected activity concentration of trapped and tumor [^{64}Cu]Cu-SARTATE versus time (in arbitrary unit) that were obtained from Eq. 5. The trapped-tracer time-activity curve (TAC; in arbitrary unit) was drawn by setting an arbitrary $\mathrm{K_{i\text{-}D}}$ value of 0.05 mL h^{-1} mL^{-1}, which does not play a role in determining its peak time (Eq. 5) [2, 4, 6]. The trapped-tracer-TAC peak time could thus be graphically assessed at 9 h post-injection, coherently with the computed outcome of $t_{\text{peak-uncorr}} = \mathrm{Log}(\alpha/\lambda_D)/(\alpha - \lambda_D)$ [2, 6]. The $t_{\text{peak-uncorr}}$ computing emphasizes the [$^{64/67}$Cu]Cu-SARTATE IF time constant α, whose 95%-CI limits obtained from fitting Dearling et al.'s mean blood-clearance data yielded a 1.1%-relative change in the peak-time value (corresponding to a 6-min-absolute change). In comparison

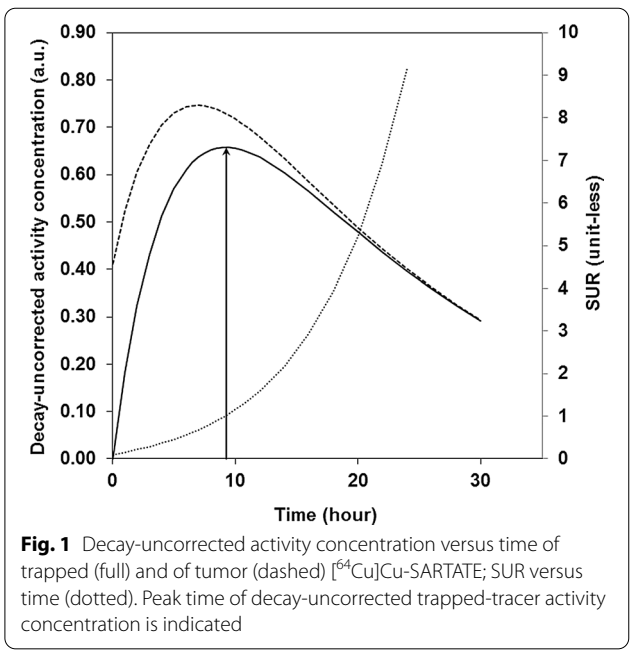

Fig. 1 Decay-uncorrected activity concentration versus time of trapped (full) and of tumor (dashed) [^{64}Cu]Cu-SARTATE; SUR versus time (dotted). Peak time of decay-uncorrected trapped-tracer activity concentration is indicated

with the trapped-tracer TAC, the tumor TAC additionally involves free tracer in blood and interstitial volume, of which fraction F_D was arbitrarily set to 0.1 mL mL^{-1}. Figure 1 also shows the corresponding SUR-versus-time curve. At $t=9$ h post-injection, the SUR value is close to 1 (for the above $K_{i\text{-}D}$ and F_D values), thus indicating that tumor- and blood-activity concentration are close, of about 27×10^3 Bq g^{-1} (for a mean [^{64}Cu]Cu-SARTATE IA of 3.61×10^6 Bq [1]). An $\pm$1-h uptake-time variability around peak time results in a +19/−17% increase/decrease in SUR, respectively.

Since the companion [$^{64/67}$Cu]Cu-SARTATE uses a "true" theranostic pair of radionuclides, resulting in chemically identical Cu-labeled SARTATE molecules, it is then assumed that $k=1$ (i.e., $K_{i\text{-}T}=K_{i\text{-}D}$) and $F_D=F_T=F$. As a consequence, an refined abbreviated equation of therapeutic [^{67}Cu]Cu-SARTATE $\tilde{A}_C$, from [^{64}Cu]Cu-SARTATE uptake in a diagnostic scan achieved at $t_{peak\text{-}uncorr}=9$ h post-injection, is:

$$\tilde{A}_{C-67Cu} = 783\times V\times IA\times[4.87\times SUR_{-64Cu}(t=9h) - 3.87\times F] \quad (6)$$

where $\lambda_D/\lambda_T=4.87$.

Discussion

In a pre-clinical intrahepatic model of NB metastatic disease representing MRD, Dearling et al. measured the biodistribution of [^{64}Cu]Cu-SARTATE and evaluated the potential of [^{67}Cu] Cu-SARTATE as a therapeutic agent [1]. In this framework, Eq. 6 allows computing of an estimate of [^{67}Cu]Cu-SARTATE $\tilde{A}_C$, and, hence, of delivered radiation-dose, involving the SUR assessed in an initial [^{64}Cu]Cu-SARTATE diagnostic scan acquired at 9 h post-injection. The assumptions made for deriving Eq. 6 are justified since [$^{64/67}$Cu]Cu-SARTATE provides the opportunity of using a "true" theranostic pair of radionuclides for which (i) $K_{i\text{-}T}=K_{i\text{-}D}$ (same irreversible trapping) (ii) $F_D=F_T$ (same fraction of free tracer in blood and interstitial volume) and (iii) same IF.

The SUR increases with time (Fig. 1), and, consequently, after/before peak time of 9 h post-injection, the SUR value involved in Eq. 6 is over/underestimated, respectively. $A\pm1$-h uptake-time variability around peak time results in a +19/−17% increase/decrease in SUR, and, hence, in an over/underestimation of [^{67}Cu] Cu-SARTATE $\tilde{A}_C$, respectively. However, Hofheinz et al. have shown in human [^{18}F]-FDG PET imaging that correcting SUR for uptake time to an arbitrary value may lead to reduced test–retest variability in comparison with that of the SUV [7]. In this connection, we suggest that, potentially, correcting SUR for uptake time (to 9 h post-injection in the current mouse framework) might provide an [^{67}Cu]Cu-SARTATE $\tilde{A}_C$ value with reduced test–retest variability.

The accuracy of the blood-activity-concentration measurements plays a critical role in the measurement uncertainty of [^{67}Cu]Cu-SARTATE $\tilde{A}_C$. Since $t_{peak\text{-}uncorr}=\mathrm{Log}(\alpha/\lambda_D)/(\alpha-\lambda_D)$, inaccurate blood-activity-concentration measurements result in an inaccurate estimate of the time constant of the [$^{64/67}$Cu]Cu-SARTATE IF (i.e., of α), and, hence, in a biased estimate of the peak-time value, leading then to the above-addressed over/underestimation of [^{67}Cu]Cu-SARTATE $\tilde{A}_C$. Furthermore, assuming $t_{peak\text{-}uncorr}$ is accurately known, an under/overestimation of [^{64}Cu]Cu-SARTATE blood-activity concentration in a mouse at peak time results in an increase/decrease in SUR, and, hence, in an over/underestimation of [^{67}Cu]Cu-SARTATE $\tilde{A}_C$, respectively. More precisely, the absolute change in [^{67}Cu]Cu-SARTATE $\tilde{A}_C$ may be assessed from Eq. 6, as:

$$\Delta A_{C-67Cu} = 783\times V\times IA\times 4.87\times(1/f-1)\times SUR_{-64Cu}(t=9h) \quad (7)$$

where f is the factor of either under- or overestimation of [^{64}Cu]Cu-SARTATE blood-activity concentration in a mouse at peak time. However, a convolutional neural network has been recently investigated in humans that can provide robust automatic image-based mean values of [^{18}F]-FDG SUV_{Blood} over the aorta. We thus suggest that such a device might also be relevant in mouse [^{64}Cu] Cu-SARTATE PET imaging to reduce the measurement uncertainty of $SUV_{Blood}(t_{peak\text{-}uncorr})$, and, hence, that of [^{64}Cu]Cu-SARTATE $SUR(t_{peak\text{-}uncorr})$ and of [^{67}Cu]Cu-SARTATE $\tilde{A}_C$ [8].

Equation 6 might be further simplified by using a mean value for F, obtained from experiments that remain to be performed. When F is considered negligible compared to $SUR_{\text{-}64Cu}$ ($t=9$ h), an overestimate of $\tilde{A}_{C\text{-}67Cu}$ is provided, that is more acceptable than an underestimate for therapeutic purpose: the higher the [^{64}Cu]Cu-SARTATE uptake, the higher the peak-time $SUR_{\text{-}64Cu}$ and the less significant the overestimation.

The scope of Eq. 6 is limited to the pre-clinical intrahepatic model of NB metastatic disease representing MRD, since mouse data published by Dearling et al. were used [1]. Therefore, the current theoretical commentary should be considered as a pre-clinical step for determining whether [^{64}Cu]Cu-SARTATE imaging might reliably predict dosimetry with [^{67}Cu]Cu-SARTATE and, hence, might predict therapeutic outcome of patients in future clinical theranostic practice. Indeed, clinical translation requires additional experiments in pre-clinical models, followed by experiments in humans to investigate the measurement uncertainty of the patient-specific [$^{64/67}$Cu]

Cu-SARTATE IF involved in $t_{peak\text{-}uncorr}$ and in $[\tilde{A}\_IF_{-T}]$, respectively, as well as that of the [^{64}Cu]Cu-SARTATE SUR possibly uptake-time corrected to $t_{peak\text{-}uncorr}$.

Conclusions

The companion [^{64}/^{67}Cu]Cu-SARTATE provides the opportunity of using a "true" theranostic pair of radionuclides, that allows deriving an abbreviated equation of therapeutic [^{67}Cu]Cu-SARTATE $\tilde{A}_C$. This equation emphasizes the [^{64}Cu]Cu-SARTATE SUR assessed in a single diagnostic scan acquired at peak time of decay-uncorrected activity concentration of trapped [^{64}Cu]Cu-SARTATE. We suggest that it might be of interest for future clinical theranostic practice.

Abbreviations

$\tilde{A}_C$: Cumulated activity; $[\tilde{A}\_IF]$: Area under curve of the tracer decay-uncorrected input function; D-RP/T-RP: Diagnostic/therapeutic radiopharmaceuticals; *F*: Fraction of free tracer in blood and interstitial volume; IF: Tracer input function; *Ki*: Tracer uptake-rate constant in tumor; λ: Tracer physical-decay-rate constant; MRD: Minimal residual disease; NB: Neuroblastoma; SUVBlood: Mean standard-uptake-value in blood; SUVTumor: Mean standard-uptake-value in tumor; SUR: Tumor-to-blood SUV ratio; TAC: Time–activity curve; *t*peak-uncorr: Peak time of decay-uncorrected trapped-tracer activity concentration; PET: Positron emission tomography.

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Authors' contributions

Study concept, EL; study design and manuscript writing, EL, HC, RM; guarantor of integrity of entire study, RM. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Not applicable.

Consent for publication

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Competing interests

The author(s) declare that they have no competing interests.

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