Distribution Volume of ^{18}F-BMS-986192 in NSCLC Patients

TO THE EDITOR: In an interesting article, Dr. Huisman et al. recently investigated the optimal kinetic model for an ^{18}F-labeled anti–programmed cell death ligand 1 (anti–PD-L1) adnectin, namely, ^{18}F-BMS-986192, to quantify PD-L1 expression in non–small-cell lung cancer (NSCLC) patients (*1*). A single-tissue-reversible (STR) compartment model, additionally including blood-volume fraction, was found to be the most preferred model for fitting the tumor time–activity curves. Its specific outcome measure is the distribution volume (V_T; mL.cm^{-3}) that is the equilibrium ratio of forward/reverse transport-rate constants, that is, K_i/k_b, between blood and reversible-trapping compartment (*2*). V_T was then used to validate simplified methods, the best correlation being obtained with body weight–normalized SUV (SUV_{BW}) at 50–80 min after injection (R^2 = 0.92–0.91), whereas a lower correlation was obtained with SUV normalized to plasma concentration (SUV/C_{plasma}, presumably at 50 min after injection; R^2 = 0.84). The authors conclude that SUV_{BW} at 60 min after injection is an accurate simplified parameter for uptake assessment of ^{18}F-BMS-986192 baseline studies.

We would like to further analyze the latter lower correlation since, under postinjection time conditions we address in this letter: (i) V_T may be assessed by the ratio of tissue/plasma tracer concentration, i.e., C_{tissue}/C_{plasma}; and (ii) the SUV_{BW}/C_{plasma} ratio may be also proportional to V_T since SUV_{BW} is proportional to C_{tissue}. To clarify this issue, we have fitted the ^{18}F-BMS-986192 input function with a triexponentially decaying function and then fitted a PD-L1–positive tumor time–activity curve by using a 3-compartment 3-parameter kinetic model (data extracted from Figs. 3 and 4 in Huisman with the Web-Plot-Digitizer software; R^2 = 0.996 and 0.998, respectively) (*1,3*). Estimates of K_i and k_b were provided, leading to the computation of V_T as K_i/k_b = 4.7 mL.cm^{-3}. This analysis also allowed us to perform both decay-corrected tissue- and decay-uncorrected trapped-tracer time–activity curves (supplemental data, available at http://jnm.snmjournals.org).

Let us first consider the rate of decay-corrected trapped tracer per tissue volume unit (at steady state): $dC_{trapped}(t)/dt = K_i \times C_{plasma}(t) - k_b \times C_{trapped}(t)$. At peak time of decay-corrected $C_{trapped}$ time–activity curve, $dC_{trapped}(t)/dt = 0$ and then $C_{trapped}(t_{peak})/C_{plasma}(t_{peak}) = K_i/k_b = V_T$. Assuming $C_{tissue}(t_{peak}) \approx C_{trapped}(t_{peak})$ (i.e., neglecting free tracer in blood and interstitial volume), t_{peak} was estimated to be 87 min from decay-corrected C_{tissue} time–activity curve, leading to C_{tissue}/C_{plasma} = 4.5 mL.cm^{-3} (versus K_i/k_b = 4.7 mL.cm^{-3}). Second, considering decay-uncorrected data, the differential equation becomes $dC_{trapped}(t)/dt = K_i \times C_{plasma}(t) - k_b \times C_{trapped}(t) - \lambda \times C_{trapped}(t)$, where λ is the ^{18}F physical-decay-rate constant. As a consequence, at peak time of decay-uncorrected-$C_{trapped}$ time–activity curve, $C_{trapped}(t_{peak})/C_{plasma}(t_{peak}) = K_i/(k_b + \lambda)$. The ratio $K_i/(k_b + \lambda)$ was calculated as 2.1 mL.cm^{-3}, whereas, at decay-uncorrected-$C_{trapped}$ t_{peak} of 53 min after injection, the ratio C_{tissue}/C_{plasma} (that may involve decay correction or not) was found to be 2.2 mL.cm^{-3}.

We therefore suggest that the SUV/C_{plasma} ratio (or, equivalently, the C_{tissue}/C_{plasma} ratio) is actually correlated with $V_T = K_i/k_b$ when assessed within 85–90 min after injection. However, the authors acknowledged that their results were only valid within 50–80 min after injection (*1*). Furthermore, we suggest that the SUV/C_{plasma} ratio assessed within 50–55 min after injection should be correlated with $K_i/(k_b + \lambda)$, instead of K_i/k_b (*1*). This alternative ratio reports on what is actually occurring at decay-uncorrected-$C_{trapped}$ t_{peak}, that is, an equilibrium between uptake and release plus physical decay. It is worth noting, regarding the part of postinjection time in its measurement uncertainty, a +13% increase occurs in the 50–55 min time range, whereas, for comparison, C_{tissue} alone, and, hence, SUV_{BW}, shows a +3% increase.

In conclusion, investigating potential clinical biomarkers and relevant simplified metrics is of upmost importance for selecting NSCLC patients who could benefit from immune checkpoint-inhibitor treatment. In ^{18}F-BMS-986192 PET imaging, Huisman et al. convincingly showed that SUV_{BW}, at 60 min after injection, may be a relevant simplified parameter to quantify tumor uptake for baseline PET studies. We additionally suggest that the ratio SUV_{BW}/C_{plasma} might be probed as a complementary possible simplified parameter, that is correlated with $K_i/(k_b + \lambda)$ within 50–55 min after injection.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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