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ARTICLE

Tissue pharmacokinetics of DHP107, a novel lipid-based oral formulation of paclitaxel, in mice and patients by positron emission tomography

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Abstract

DHP107 is a newly developed lipid-based oral formulation of paclitaxel. We evaluated the in vivo tissue pharmacokinetics (PKs) of DHP107 in mice and patients using positron emission tomography (PET). Radioisotope-labeled [^{3}H]DHP107 and [^{18}F]DHP107 for oral administration were formulated in the same manner as the manufacturing process of DHP107. In vivo tissue PK were assessed in healthy ICR mice and breast cancer xenografted SCID mice. Two patients with metastatic breast cancer were clinically evaluated for absorption at the target lesion after internal absorbed dose estimation. Whole-body PET/computed tomography data were acquired in healthy and xenografted mice and in patients up to 10–24 h after administration. Tissue [^{18}F]DHP107 signals were plotted against time and PK parameters were determined. The amounts of radioactivity in various organs and excreta were determined using a beta-counter and are expressed as the percentage of injected dose (ID). Oral

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[^{18}F]DHP107 was well-absorbed and reached the target lesion in mice and patients with breast cancer. Significant amounts of radioactivity were found in the stomach, intestine, and liver after oral administration of [^{3}H]- and [^{18}F]DHP107 in healthy mice. The [^{18}F]DHP107 reached a peak distribution of 0.7–0.8%ID in the tumor at 5.6–7.3 h in the xenograft model. The [^{18}F]DHP107 distribution in patients with metastatic breast cancer was the highest at 3–4 h postadministration. Systemic exposures after administration of a DHP107 therapeutic dose were comparable with those in previous studies. PET using radioisotope-labeled drug candidates is useful for drug development and can provide valuable information that can complement plasma PK data, particularly in early phase clinical trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

PET allows visualizing and quantifying the tissue pharmacokinetic properties of a drug throughout the body.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the tissue pharmacokinetic profile of DHP107, a novel oral paclitaxel, when administered with [^{18}F]DHP107 to mice and humans with breast cancer?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

PET/CT studies enabled for evaluating the relative amount and its time profile of orally administered [^{18}F]DHP107, distributed to each organ and tissue, in mice and patients with breast cancer. In a clinical trial with two metastatic breast cancer patients, oral [^{18}F]DHP107 was well absorbed and its localization in the tumor lesion was successfully visualized.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

PET/CT imaging using radioisotope-labeled drug candidates can provide information on drug properties by exploring the tissue pharmacokinetics in early drug development.

INTRODUCTION

Paclitaxel is a clinically effective, but water-insoluble antitumor drug that is active against a broad spectrum of solid cancers, including lung, liver, and breast cancers. It is a substrate of P-glycoprotein (P-gp), an efflux transporter in the gastrointestinal epithelium.[1] Therefore, paclitaxel was originally developed and is used as an i.v. formulation. However, the oral administration route is preferable for convenience and sustained exposure, which is more important than achieving a high concentration for the efficacy of cell-cycle phase-specific agents, such as paclitaxel.[2]

DHP107 (Liporaxel; Daehwa Pharmaceutical, Korea) is a novel lipid-based oral formulation of paclitaxel. DHP107 is lipid-soluble and is systemically absorbed without the need for P-gp inhibitors or Cremophor EL.[3] DHP107 is feasible, safe, and effective in patients with advanced malignancies refractory to standard treatments.[4,5] DHP107 was efficacious in patients with metastatic solid tumors and recurrent gastric cancer in phase I/IIa and III studies.[6,7] Furthermore, the interindividual variability of paclitaxel exposure after DHP107 was comparable to that of paclitaxel injection; the coefficient of variation of the area under the concentration-time curve until the last measurable concentration (AUC_{last}) of paclitaxel after administration of DHP107 (60–600 mg/m^2) ranged from 11.8 to 34.0%, which was close to the 24.4% for i.v. paclitaxel at 175 mg/m^2.[4]

Drug concentrations in the blood may not reflect those in tissues. If concentrations in blood and tissues are available, tissue–blood pharmacokinetic (PK) modeling may help optimize the drug dosage regimen. However, the in vivo time-course of DHP107 in tissues, particularly in the target tissue (i.e., tumors), has not been studied in humans.

Positron emission tomography (PET) studies using radioisotope-labeled drugs have an advantage over conventional PK studies in evaluating tissue PKs.[8–10] The exceptional sensitivity of PET and the excellent temporal and spatial resolution of PET images allow visualizing and quantifying tissue PK properties of drugs throughout the body, including specific target organs and lesions.[9,11–13]

In the current study, we examined the tissue PKs of DHP107 in mice using PET after oral administration of [^{18}F]

DHP107, which was in clinical trial at the time. We analyzed [^{3}H]DHP107 distribution in mice using a beta-counter to validate the PET PKs of [^{18}F]DHP107 and methodological limitations that can be argued for whether PKs are equivalent between microdose and therapeutic doses are discussed based on the results obtained from experimental validation. An exploratory PET clinical trial was conducted in patients with hormone receptor (HR)-positive and HER2-negative metastatic breast cancer to determine whether the findings in preclinical assessment could be extrapolated to humans.

MATERIALS AND METHODS

Preparation of [^{18}F]DHP107 and [^{3}H]DHP107

[^{18}F]Paclitaxel was prepared by conventional Kryptofix-mediated nucleophilic aromatic ^{18}F-substitution on the trimethylammonium triflate-leaving group of the precursor through three steps (Figure S1) in the modified TRACERlab FX N Pro module (GE Healthcare; Figure S2), with a slight modification according to the literature.[14,15] For formulation of [^{18}F]paclitaxel for oral administration (named [^{18}F]DHP107), finally obtained absolute ethanol solution containing [^{18}F]paclitaxel (~370 MBq/0.1 ml) was mixed with glyceryl monooleate. After vortexing for 10 s, most of the ethanol was removed by nitrogen gas streaming at 40°C for 20 min, and then, glycerin fatty acid ester and polysorbate 80 were added sequentially. All formulation processes were the same as for the manufacturing of DHP107. For the clinical study, the process was carried out in a biosafety cabinet with real-time environmental monitoring of airborne particles in 1 m^3 air and microbial contaminations (air sample, settle plates, contact plates, and glove print 5 fingers). Preparations were carried out in a grade A environment. Quality assays for the clinical study met the criteria set by the Korean Ministry of Food and Drug Safety (MFDS), including visual inspection, foreign insoluble matter test, radionuclide identity, radiochemical and chemical purities, and determination of radioactive concentration. Next, to obtain [^{3}H]paclitaxel for oral administration (named [^{3}H]DHP107), it was manufactured using [^{3}H]paclitaxel in ethanol (purity: >97%, specific activity: 20–40 Ci/mmol; Moravek) according to the [^{18}F]DHP107 manufacturing process described above.

Animals

Animal studies were conducted in accordance with institutional guidelines, and protocols were approved by the Animal Ethics Committee of Seoul National University Bundang Hospital (BA1608-206/049-01, August 9, 2016). To study the in vivo tissue PK of [^{18}F]- and [^{3}H]DHP107, 6-week-old female ICR mice (Orient Bio, Gyeonggi-do, Korea) were used. The mice were housed individually, with ad libitum access to water and food (AIN 93G formula) in a controlled environment (24 ± 2°C, 40 ± 2% humidity, 12-h light/dark cycle). To study target tissue (i.e., tumor) PK, HER2-overexpressing SK-BR3 tumor-bearing SCID mice (Orient Bio) were used.

Human participants

An open-label, exploratory clinical study was conducted in two patients with metastatic breast cancer who received a single oral dose of DHP107 at 200 mg/m^2 and [^{18}F]DHP107 with a radioactivity of 185–555 MBq at a microdose (0.98–2.9 μg calculated from molar activity). Written informed consent was obtained from the patients. Patients aged greater than 19 years, diagnosed with solid cancer on histopathology or cytology, and with progressed, metastatic, or recurrent disease despite standard therapies for solid tumors were eligible. The disease had to be measurable according to the Response Evaluation Criteria in Solid Tumors version 1.1. The Eastern Cooperative Oncology Group performance status should be less than 2 and the expected survival time should be greater than or equal to 12 weeks. The study protocol was approved by the MFDS and the Institutional Review Board of Seoul National University Bundang Hospital (B-1706/403-001, ClinicalTrials.gov identifier: NCT04046016).

Preclinical PET study

After fasting around 9 h (free access to water), [^{18}F]DHP107 (10.9 ± 0.29 MBq in 0.1 mL) was orally administered to ICR mice (22.2 ± 0.3 g, n = 6, 10.9 ± 0.38 MBq/0.1 ml, co-administered with 50 mg/kg of DHP107) and SK-BR3 tumor-bearing SCID mice (G1; 17.2 ± 0.9 g, n = 4, 10.8 ± 0.63 MBq/0.1 ml for therapeutic-dose group co-administered with 50 mg/kg of DHP107 and G2; 17.6 ± 1.4 g, n = 4, 10.3 ± 0.87 MBq/0.1 ml for micro-dose group without DHP107, respectively) using a disposable feeding needle coupled with a 1-ml syringe. Whole-body PET/computed tomography (CT) data were acquired at 0.5, 1, 3, 7, and 12 h postadministration (up to 24 h for ICR mice). The [^{18}F]DHP107 distribution was determined using whole-body PET images, and time–radioactivity profiles were generated for each organ of interest. Canvas images of volume-of-interest (VOI) drawings were chosen between CT and PET images, depending on organ visibility and mobility. VOIs for the liver, lungs, spleen, brain, stomach, heart, and kidneys were drawn on CT images of individual subject in a slice-by-slice manner, whereas those for the gallbladder, intestine, and urinary bladder were drawn on averaged PET images by adjusting iso-contour VOIs. The amount of radioactivity in each organ was calculated as the % injected dose (ID) using the following

formula: %ID = ([total amount of radioactivity in organ]/[amount of radioactivity orally administered]) × 100. The following PK parameters of [^{18}F]DHP107 in each organ were quantitatively assessed based on the time–concentration profiles of the organs of interest: peak concentration (C_{max}), time to reach C_{max} (T_{max}), terminal half-life ($t_{1/2}$), and AUC from time 0 to 24 h ($AUC_{0–24\,h}$). PET image analysis was performed using PMOD software version 3.1 (PMOD Technologies, Zurich, Switzerland). PK parameters were calculated using GraphPad Prism version 8.0 (GraphPad Software).

Clinical PET study

After a greater than 6-h water fast, subjects were brought to the PET center of Seoul National University Bundang Hospital 2 h before the scan. Head and limbs were fastened to prevent movement during the scan. Subjects underwent five whole-body PET scans at 0.5, 2, 4, 8, and 10 h after oral administration of microdose [^{18}F]DHP107 and therapeutic dose of DHP107 (200 mg/m^2, the dose used in phase III).[7] The administered radioactivity of [^{18}F]DHP107 was 418.1 MBq for one subject and 290.0 MBq for the other. The injected mass of [^{18}F]DHP107 was ~ 2.22 μg and 1.54 μg, respectively, calculated from the molar activity at the end of synthesis. A low-dose helical CT scan was conducted prior to the PET scan. Measurement of [^{18}F]DHP107 distribution for each organ of interest was performed in the manner previously described. The radioactivity concentration of [^{18}F]DHP107 in organs was expressed as %ID, and C_{max}, T_{max}, and AUC were estimated. $T_{1/2}$ was estimated by nonlinear least square curve fitting using the multiple exponential function in GraphPad Prism version 8.0.

For plasma PK analysis, blood samples were collected using sodium-heparin-laced tubes at 0, 2, 4, 8, and 10 h after administration. Plasma concentrations of DHP107 were determined by liquid chromatography-tandem mass spectrometry using an Agilent 260 Infinity system (Agilent Technologies) and API4000 (AB SCIEX). Standard curves for DHP107 were linear over 0.75–600 ng/ml, with a lower limit of quantification of 0.75 ng/ml. The C_{max}, T_{max}, AUC from 0 to the last measurable time (AUC_{last}), AUC from 0 to infinity (AUC_{inf}), and $t_{1/2}$ were estimated by the noncompartmental method using Phoenix WinNonlin version 8.0.

Internal dosimetry of experimental animals

Internal dosimetry of experimental animals was performed using an image-based approach with the Monte Carlo N-Particle Code, according to ref. 16 Based on PET images at 0.5, 1, 3, 7, 12, and 24 h after oral administration (ICR mice, 22.2 ± 0.3 g, n = 6, 10.9 ± 0.38 MBq), the residence time was calculated based on the time-activity curve of region-segmented PET data. The human absorbed dose of [^{18}F]DHP107 for approval of exploratory PET clinical trial from the MFDS was estimated by the adult S value and its residence times.

Beta-counter study

The ex vivo biodistribution of [^{3}H]DHP107 at a therapeutic dose was assessed using ICR mice (21.9 ± 0.4 g, n = 4 at each point; 0.5, 1, 2, 4, 8, 12, 24, and 48 h after administration). After a greater than 9-h water fast, [^{3}H]DHP107 (0.93 MBq/0.1 ml, co-administered with 50 mg/kg of DHP107) was orally administered using a disposable feeding needle. The animals were killed by cervical dislocation at the indicated timepoints, and organs were harvested. Another 6 animals were used to evaluate the amount of radioactivity excreted via the feces and urine for 48 h after oral administration of [^{3}H]DHP107 (25 μCi/100 μl) at a therapeutic dose. Feces and urine were collected every 12 h using cleaning wipes. Radioactivity in the dissected organs and excreta was measured using a beta-counter after homogenization and dilution with a cocktail solution to amplify the signal. The amount of radioactivity was expressed as %ID.

RESULTS

Preparation of [^{18}F]DHP107 and [^{3}H]DHP107

The [^{18}F]paclitaxel was synthesized by nucleophilic aromatic substitution by fluorine-18 on pentamethylbenzyl trimethylammoniumbenzoate, followed by hydrolysis with lithium hydroxide to obtain [^{18}F]fluorobenzoic acid. Treatment of [^{18}F]fluorobenzoic acid and *N*-debenzoyl paclitaxel with *N*,*N*-diisopropylethylamine and diethyl cyanophosphonate resulted in amide formation to the desired [^{18}F]paclitaxel. The total time for radiosynthesis was ~ 110 min, and the radioactivity yield after high-performance liquid chromatography purification was 6.8 ± 1.6% (Figure S3, n = 24, non-decay-corrected). The radiochemical purity was greater than 99%, and the identity was confirmed by co-injection with standard paclitaxel (Figure S4). The specific radioactivity at the end of synthesis was 164 ± 39 GBq/μmol. No significant radiolysis of [^{18}F]paclitaxel in absolute ethanol was observed after 4 h at room temperature. Similarly, [^{18}F]DHP107 showed no significant radiolysis after 2 h at room temperature. The [^{18}F]DHP107 used in the clinical study met the quality control criteria for clinical studies set by the MFDS (Table S1). The [^{3}H]DHP107, obtained following the [^{18}F]DHP107 process from [^{3}H]paclitaxel dissolved in ethanol, was not notably different from [^{18}F]DHP107.

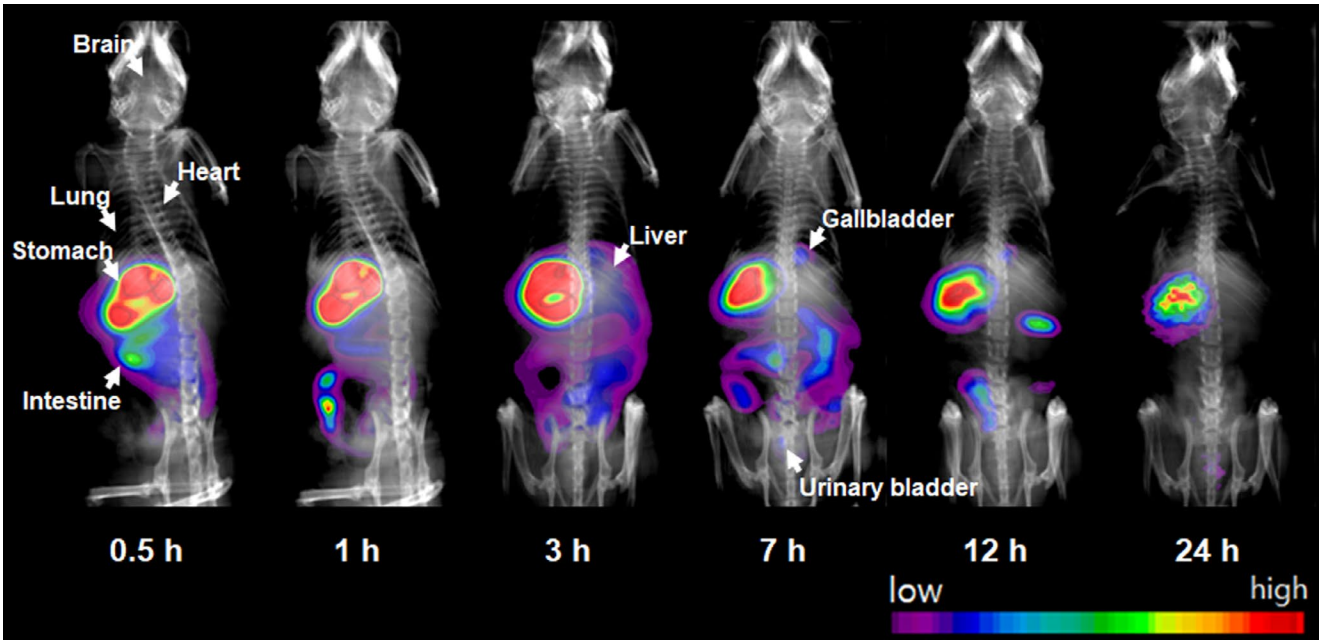

FIGURE 1 Representative whole-body positron emission tomography/computed tomography images of [^{18}F]DHP107 at various time points after oral administration in healthy mice

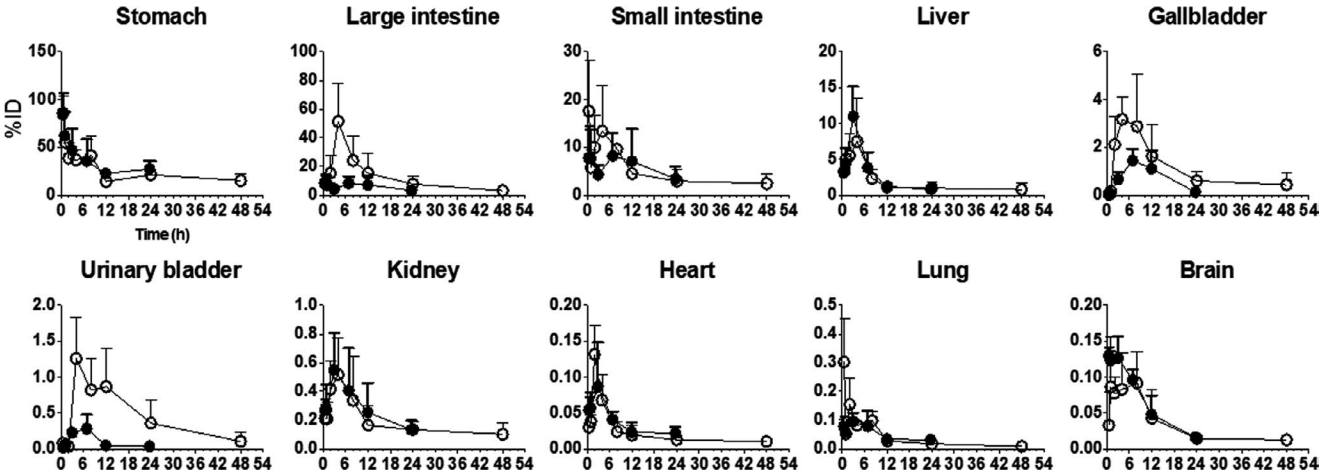

FIGURE 2 Time-concentration profiles of oral [^{18}F]DHP107 (●) and [^{3}H]DHP107 (○) in organs of interest in healthy mice. %ID, percentage of injected dose

Preclinical In Vivo tissue PK

Initially, [^{18}F]DHP107 was mostly accumulated in the stomach ($AUC_{0-24\ h}$ = 749.3 ± 86.4%ID h) (Figures 1, 2 and Table S2). The $AUC_{0-24\ h,\ stomach}/AUC_{0-24\ h,\ remaining\ organs}$ was 0.8. The [^{18}F]DHP107 had a $t_{1/2}$ of 27.3 ± 6.4 h in the stomach. The order in the distribution of [^{18}F]DHP107 was as follows: stomach, intestine, liver, gallbladder, kidneys, bladder, brain, lungs, and heart. Within 3 h of administration, the [^{18}F]DHP107 concentration was the highest in the liver (C_{max} = 11.0% ID, T_{max} = 2.9 h), kidneys (C_{max} = 0.7% ID, T_{max} = 2.8 h), lungs (C_{max} = 0.1% ID, T_{max} = 2.8 h), and heart (C_{max} = 0.1%ID/g, T_{max} = 1.8 h) except for the stomach, the route of the administration. [^{18}F]DHP107 was distributed in most organs and was eliminated with the organs' association and dissociation rates. A significant amount of radioactivity was distributed to the intestine, gallbladder, and liver, and oral [^{18}F]DHP107 was shown to undergo hepatic metabolism and to be excreted via the biliary route ($AUC_{0-24\ h}$, gallbladder = 18.6%ID h). Of the total amount of orally administered [^{18}F]DHP107, 16.1% (= $AUC_{0-24\ h,\ intestine+gallbladder}/AUC_{0-24\ h,\ total\ organs}$ ×100%) was excreted via the biliary route, whereas only ~ 0.9% (= $AUC_{0-24\ h,\ urinary\ bladder+kidneys}/AUC_{0-24\ h,\ total\ organs}$ ×100%) was excreted in the urine

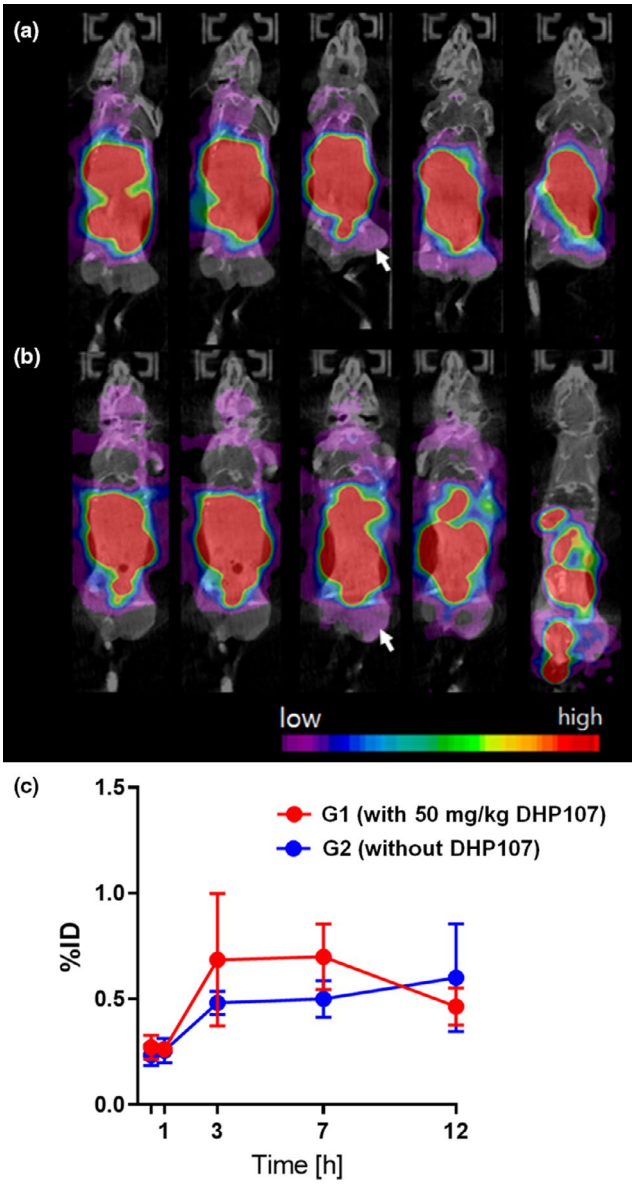

FIGURE 3 Representative whole-body positron emission tomography (PET)/computed tomography (CT) images and time course of oral [^{18}F]DHP107 distribution in tumor-bearing mice; arrows indicate tumor location. (a) PET/CT images of [^{18}F]DHP107 with therapeutic dose of DHP107. (b) PET/CT images of microdose [^{18}F]DHP107 without DHP107. (c) Timecourse of [^{18}F]DHP107 distribution in tumor. %ID, percentage of injected dose

(Table S2). The in vivo tumor PKs of [^{18}F]DHP107 in HER2-overexpressing SK-BR3 subcutaneous xenograft-bearing SCID mice were successfully visualized and assessed by PET (Figure 3). The [^{18}F]DHP107 attained peak distribution to the tumor with C_{max} of 0.80%ID and 0.66%ID and T_{max} of 5.67 h and 7.33 h in G1 (+10 mg/kg DHP107) and G2 (without DHP107), respectively. Regardless of the co-administration of DHP107, the total accumulation of radioactivity was comparable between G1 and G2, with $AUC_{0-12\,h}$ of 6.83%ID h and 5.64%ID h, respectively (Table S3).

Preclinical Ex Vivo tissue PK

The [^{3}H]DHP107 was mostly distributed to the stomach ($AUC_{0-48\ h}$ = 1078.0%ID h) early after oral administration (Figure 2 and Table S4). The $AUC_{0-48\ h,\ stomach}$/$AUC_{0-48\ h,\ remaining\ organs}$ was 0.5. The [^{3}H]DHP107 had a $t_{1/2}$ of 36.1 h in the stomach. The order in the distribution of [^{3}H]DHP107 was similar to that of [^{18}F]DHP107. In all organs other than the stomach, $t_{1/2}$ was 9–60 h. Significant amounts of radioactivity were found in the intestine, gallbladder, and liver, and oral [^{3}H]DHP107 appeared to undergo hepatic metabolism and to be excreted via the biliary route ($AUC_{0-48\ h,\ gallbladder}$ = 53.4%ID h; Table S4). Approximately 50% of [^{3}H]DHP107 was excreted via the feces and urine by 48 h after administration.

Absorbed dose calculation

The highest absorbed dose was detected in the stomach, with 6.15E-02 mSv/MBq (Table S6). The effective doses of [^{18}]F-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG), most widely used clinically in nuclear medicine, and [^{18}F]DHP107 in adults are 4.64E-02 mSv/MBq and 6.56E-02 mSv/MBq, respectively.[17] The radiation dose of [^{18}F]DHP107 was slightly higher than that of [^{18}F]FDG, but it might be safe at a similar dose.

In Vivo tissue PK in patients with metastatic breast cancer

The age and weight of two female subjects were 70 and 62 years old, 56.0 and 59.4 kg, respectively. In the patient with metastatic lesions in the sternum, right paratracheal lymph nodes, lungs, right seventh and eighth ribs, and T-spines, [^{18}F]DHP107 distribution was the highest at 4.7 h, with the largest tumor lesion found in the sternum (Figure 4A). In the left lower-lobe lung metastasis, peak distribution was achieved readily (i.e., at the first time point) after administration. In the patient with tumors in the left breast, other tumors in the right breast, and metastases to the liver and right kidney, [^{18}F]DHP107 distribution was the highest at 4.7 and 8.9 h in both primary breast tumor lesions (Figure 4B). In both patients, [^{18}F]DHP107 was predominantly distributed in the stomach and intestine. The kidneys, lungs, and heart had less than 4.0%ID at all timepoints (Figure 4C, Table S7). [^{18}F]DHP107 uptake by major organs and tissues was similar to that in the preclinical studies.

DHP107 plasma concentrations exceeded the lower limit of quantification until 10 h after administration in both patients. DHP107 was rapidly absorbed with T_{max} of 2.0 and 2.25 h and C_{max} of 373.2 and 538.8 ng/ml, respectively. The plasma $t_{1/2}$ of DHP107 was 2.0–2.5 h (Table S8).

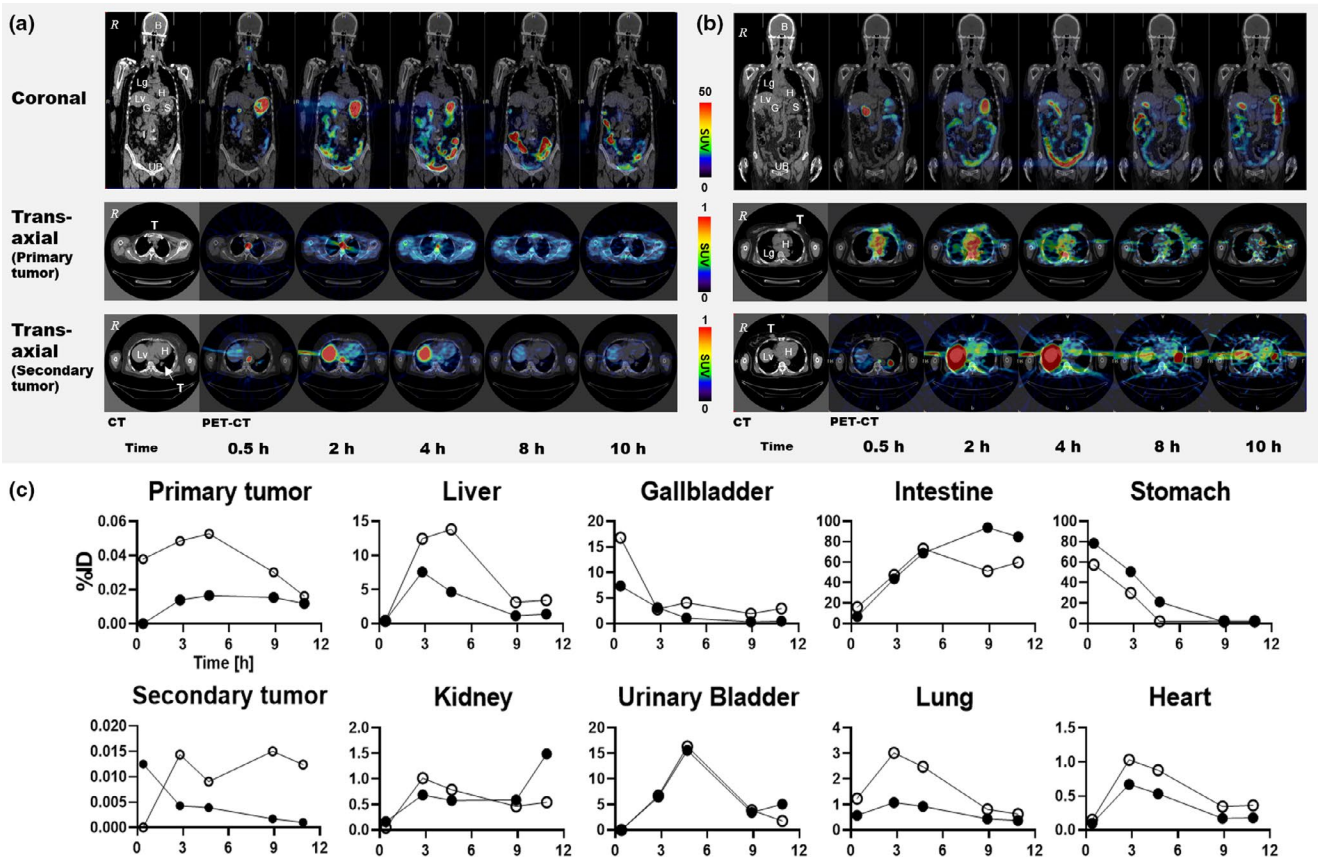

FIGURE 4 Representative whole-body positron emission tomography (PET)/computed tomography (CT) images and timecourse of oral [^{18}F]DHP107 distribution in clinical subjects (B, brain; Lg, lungs; H, heart; Lv, liver; G, gallbladder; S, stomach; I, intestine; UB, urinary bladder; T, tumor; R, right). All values are decay-corrected for the physical half-life of F-18. (a) PET/CT images of [^{18}F]DHP107 in subject 1. (b) PET/CT images of [^{18}F]DHP107 in subject 2. (c) Timecourse of oral [^{18}F]DHP107 distribution in clinical subjects (●, subject 1; ○, subject 2). %ID, percentage of injected dose

Safety and tolerability

The patients received 10 and 9 cycles of DHP107 therapy, respectively, and both achieved clinical benefit (stable disease >6 months). Each cycle was 28 days, and 200 mg/m^2 of DHP107 was administered twice daily on days 1, 8, and 15. DHP107 was tolerated well, without serious adverse events. The adverse events included grade 1 and 2 peripheral neuropathy, paronychia, alopecia, myalgia, skin rash, and diarrhea. Grade 3 neutropenia was the only grade 3/4 adverse event.

DISCUSSION

Information on drug absorption, distribution, metabolism, and excretion is imperative for understanding PK properties after administration. To predict drug safety and effectiveness, it is important to gather information on drug distribution by determining the extent to which drugs migrate from the blood to tissues and cells, and the extent to which they reach systemic organs, target organs, and tissues. As drug distribution and behavior cannot easily be observed in vivo, information is generally inferred from drug concentrations in the blood. Bioimaging technologies, such as PET, have attracted attention for evaluating drug distribution in vivo.[5,11,13,18] Our study demonstrated the utility and uniqueness of PET in drug development, particularly in early clinical trials and proof-of-concept studies. PET is firmly established as a key three-dimensional medical imaging technique in the clinic.[19] PET with radioisotope-labeled drugs can provide PK information that cannot be obtained from conventional blood PK studies.

DHP107 is a lipid-based oral paclitaxel formulation. Paclitaxel i.v. is widely used alone or in combination for the treatment of various cancers, but it has limited absorption and causes side effects and patient discomfort. DHP107 is expected to have increased drug absorption, less side effects, and easier administration than existing formulations. We investigated the systemic distribution of DHP107 by administering a therapeutic dose of DHP107 containing [^{18}F]DHP107 in tumor-bearing mice and patients with metastatic breast cancer. The utility of PET/CT bioimaging after the administration of radioisotope-labeled drugs was evaluated.

We successfully labeled DHP107 with ^{3}H and ^{18}F and orally administered these formulations in mice and patients ([^{18}F]DHP107 only in the latter). PET/CT images adequately showed the distribution of radioisotope-labeled DHP107 in organs and target tissues. In accordance with findings in previous studies, we demonstrated that oral DHP107 was absorbed and distributed in target organs in mice.[18,19] In patients with metastatic breast cancer, DHP107 was well-absorbed through the intestinal tract and steadily reached tumor lesions, and the drug was well-tolerated at a 200 mg/m^2 dose. Taken together, our results demonstrate that DHP107 is well-tolerated and readily absorbed through the gastrointestinal tract, reaches the target lesion, and exhibits clinical anticancer efficacy, as shown in a clinical study.[7]

The in vivo tumor PK of oral [^{18}F]DHP107 and i.v. [^{18}F]paclitaxel in HER2-overexpressing SK-BR3 subcutaneous xenograft mice were visualized and quantitatively assessed by PET. Oral [^{18}F]DHP107 accumulated in the tumors for 12 h ($AUC_{0–12\ h}$ = 5.66%ID h) and reached the highest distribution concentration with C_{max} = 0.66%ID and T_{max} = 7.33 h. In contrast, the tumor distribution of i.v. [^{18}F]paclitaxel decreased immediately after until 12 h after administration, from 0.6%ID to 0.2%ID, resulting in an $AUC_{0–12\ h}$ of 3.86%ID h (Table S9). The greater AUC for oral DHP107 than for i.v. [^{18}F]paclitaxel suggests that DHP107 may have a superior targeting ability in HER2-overexpressing tumors and that this drug, which has been approved by the MFDS for gastric cancer, may also be used for the treatment of HER2-positive breast cancer.

Plasma PK analysis revealed that DHP107 was well-absorbed in patients with metastatic breast cancer (T_{max} = 2–2.5 h), which was consistent with findings in a previous human PK study (T_{max} = 2.4–3.6 h).[4] However, the plasma $t_{1/2}$ of DHP107 was 2.0–2.5 h, which was substantially shorter than that in the previous study (15.3–24.2 h). This is probably because we collected blood samples only up to 10 h after dosing, as opposed to the 48 h postadministration in the previous study. In addition, according to our previous report, the PK parameters, such as T_{max}, C_{max}, and AUC, of paclitaxel based on high-performance liquid chromatography (HPLC) using a semimicro-HPLC system in each organ was similar to that of paclitaxel acquired by PET.[19]

Nevertheless, our study had limitations. First, clinical PK evaluation was conducted only in two patients, and only for HR-positive HER2-negative metastatic breast cancer. However, tissue distribution images were clearly and consistently obtained in both patients and confirmed that oral DHP107 reached the target lesions. Second, the number of subjects was too small to generalize the efficacy of DHP107. However, it is very likely that patients will benefit from DHP107 because it reaches the target lesion and its anticancer efficacy has been demonstrated.[5,20] Finally, in the present study, no serious adverse event was reported from the participants. Radiation exposure demanding potential hazardous to the participants by [^{18}F]DHP107 administered orally (effective dose: 1.41E-02 mSv/MBq, equally for both patients) was comparable to the average effective dose from whole-body [^{18}F]FDG administration (Table S10).

CONCLUSIONS

[^{18}F]DHP107 was well-absorbed through the gastrointestinal tract following oral administration, accumulated in the target lesion in mice and patients with breast cancer, and was found to be safe. This study showed that PET using radioisotope-labeled drug candidates is useful in drug development and can complement plasma PK data, especially in early clinical trials.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

B.S.M., H.S.P., J.S., J.H.K., S.E.K., and H.L. wrote the manuscript. B.S.M., H.S.P., J.S., J.H.K., S.E.K., and H.L. designed the research. B.S.M., H.S.P., J.S., J.H.K., S.E.K., H.L., I.H.L., A.K., S.J.M, Hc.L., M.H.S., S.B.K., S.M.P., S.K.W., J.H.J., and B.S.K. performed the research. B.S.M., H.S.P., J.S., S.B.K., S.M.P., and S.K.W. analyzed the data. B.S.M., H.S.P., J.S., J.H.K., S.E.K., and H.L. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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