Cancer Investigation, Early Online:1–7, 2015
ISSN: 0735-7907 print / 1532-4192 online

DOI: 10.3109/07357907.2015.1081691

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ORIGINAL ARTICLE

A Phase 1, Multi-Center, Open-Label, Dose-Escalation Study of ^{131}I-CLR1404 in Subjects with Relapsed or Refractory Advanced Solid Malignancies

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This study explores the imaging and therapeutic properties of a novel radiopharmaceutical, ^{131}I-CLR1404. Phase 1a data demonstrated safety and tumor localization by SPECT-CT. This 1b study assessed safety, imaging characteristics, and possible antineoplastic properties and provided further proof-of-concept of phospholipid ether analogues' retention within tumors. A total of 10 patients received ^{131}I-CLR1404 in an adaptive dose-escalation design. Imaging characteristics were consistent with prior studies, showing tumor uptake in primary tumors and metastases. At doses of 31.25 mCi/m^2 and greater, DLTs were thrombocytopenia and neutropenia. Disease-specific studies are underway to identify cancers most likely to benefit from ^{131}I-CLR1404 monotherapy.

Keywords: Phase 1, Radiotherapy, Targeted therapy, Drug discovery

INTRODUCTION

Targeted radiopharmaceutical therapy (TRT) is an attractive cancer treatment option because of its potential to deliver cytotoxic doses of radiotherapy to specific cellular or anatomic targets. Preliminary success in TRT was achieved with the FDA approval of I-131-tositumomab (Bexxar, GlaxoSmith-Kline, Philadelphia, PA, USA) (1, 2), Y-90-/In-111-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Henderson, NV, USA) (3), and radium-223 dichloride (Xofigo, Bayer, Leverkusen, Germany) (4, 5). Each of these compounds has demonstrated tissue specificity and anti-tumor efficacy for specific cancers or anatomic locations. Although approved, each radiopharmaceutical listed above has a somewhat limited clinical spectrum and several toxicities common to all including bone marrow suppression. Exploiting a cellular target that is more broadly applicable to multiple tumor types in any anatomic location may present significant opportunities for detecting and treating malignancies.

Cancer cells contain higher quantities of naturally occurring, membranous ether lipids than normal cells (6, 7). When it was demonstrated that tumor tissue had lower ether cleavage enzyme activity than normal tissue, it was hypothesized that this difference accounted for the accumulation of ether lipids in tumor cells (8). These observations led to increased interest in phospholipid ethers (PLE), a minor subclass of phospholipids present in mammalian cell membranes which constitute a small component of the total phospholipid content.

PLE analogs have been shown to be selectively retained in tumors, generating interest in their potential as imaging and anti-tumor agents. The tumor-selective uptake of PLE analogs and structurally related molecules called alkylphospholipids is due in part to their insertion into areas of the cell membrane that contain large accumulations of sphingolipids and cholesterol known as lipid rafts that are internalized into the cell and accumulate in perinuclear structures (9–16). Tumor cells have been shown to have six- to ten-fold greater amounts of membrane lipid rafts compared to normal cells (17–20).

Studies of several PLE analogs in rodent models identified CLR1404 as the best PLE for tumor-imaging. Tumor-specific uptake and prolonged tumor retention of CLR1404 has been demonstrated in more than 50 spontaneous and xenograft tumor models. Coupling a tumor-specific compound with a radioisotope with proven anticancer efficacy was hypothesized to have unique imaging and therapeutic potential (21). ^{131}I has a decades-long track record of safety and efficacy in thyroid cancer, where tissue-specific delivery is assured (22–27). Because of its history, safety, and efficacy across a variety of clinical presentations, ^{131}I was chosen as the isotope to couple to CLR1404. ^{131}I-CLR1404 potently inhibited tumor growth

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Received 30 June 2015; accepted 06 August 2015.

in a series of murine tumor models, which provided the theoretical underpinnings for its use in therapeutic trials (21).

An initial phase 1a dosimetry trial (DCL-08-001; NCT00925275) of ^{131}I-CLR1404 was conducted in eight subjects with advanced cancers. Each subject received a single 10 millicurie (mCi) infusion of study drug. Peak plasma concentrations (C_{max}) were observed at 5 minutes after infusion and then declined in a bi-exponential manner, with a mean elimination half-life of 822 hours. Imaging data from this study showed tumor-specific uptake and retention in multiple different tumor types. ^{131}I-CLR1404 was well tolerated with five Grade 1 drug-related adverse events observed. Dosimetric analysis determined that a 20 mCi dose (12.5 mCi/m^2 for a subject with a body surface area of 1.6 m^2) is needed to deliver 35–40 cGy to the bone marrow, chosen because it is one-fifth of the assumed tolerance of the bone marrow (28).

Based on these data, ^{131}I-CLR1404 was examined in a follow-up phase 1b, multi-center study, with a starting dose of 12.5 mCi/m^2, to determine a recommended dose of ^{131}I-CLR1404 for treating advanced solid malignancies and to further characterize this agent's safety and pharmacokinetic profile, anti-tumor activity, and tumor imaging capabilities.

MATERIALS AND METHODS

Study design

This was a phase 1, multi-center, open-label, dose-escalation study of ^{131}I-CLR1404 conducted in two phases: dosimetric phase and treatment phase. The primary objective of the study was to determine the recommended dose of ^{131}I-CLR1404 for the treatment of subjects with advanced solid malignancies. Secondary objectives were to expand ^{131}I-CLR1404's safety and pharmacokinetic profile and determine its preliminary anti-tumor activity. A subset of patients with nonhepatic primary tumors also had single photon emission computed tomography (SPECT) or SPECT/computed tomography (CT) imaging. ^{131}I-CLR1404 was provided by Cellectar Biosciences, Inc. (Madison, WI, USA) for this study. The study (clinicaltrials.gov identifier, NCT01495663) was reviewed and approved by each center's Institutional Review Board, and all patients signed informed consent prior to enrollment.

Patients

Adult patients with relapsed or refractory advanced solid malignancies, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, ECOG performance status 0–2, an estimated life expectancy of at least 4 months and adequate bone marrow, cardiac, renal and hepatic function were eligible for this study.

Patients were excluded from enrollment if they had received more than three prior cytotoxic chemotherapy regimens or had radiation, chemotherapy, or other investigational agents within 4 weeks of the start of study. Patients who received blood transfusions or hematopoietic growth factor therapy within 30 days of study start, had prior stem cell transplantation, had uncontrolled hypertension, cardiac, or peripheral vascular disease, had HIV or viral hepatitis, or had active infections were excluded. All patients provided written informed consent at screening.

Treatment

Within 14 days of screening evaluation, eligible, consented subjects were enrolled in the dosimetry phase of the study (days D0–D6). Each subject received a single 5 mCi dosimetric dose of the study drug on dosimetry day D0. All subjects were prescribed thyroid protection medication to be taken 24 hours prior to the dosimetric dose and continued daily for 14 days after the therapy dose. Thyroid protection medication included one of the following: saturated solution of potassium iodide drops, Lugol's solution, or potassium iodide tablets. Each institution used their discretion in the choice of thyroid protection used. Radiation safety protocols were reviewed and adhered to as dictated by each institution's radiation safety officer.

Anterior and posterior ^{131}I whole body planar scans were conducted on dosimetry days D0, D1, D2, D3, and D6 and were reviewed by a nuclear medicine investigator on day D6. Subjects with ^{131}I-CLR1404 biodistribution that showed uptake in tumors and did not show significant off-target distribution (e.g. lung parenchyma, myocardium) were eligible to enroll in the treatment phase.

At the beginning of the treatment phase (days T0-T56), each patient received a single infusion of ^{131}I-CLR1404 over approximately 30 minutes. The first cohort of subjects received a dose of 12.5 mCi/m^2 with BSA calculated from actual body weight but not exceeding 2.5 m^2. For determination of the recommended dose, dose escalation and de-escalation was in full increments of 12.5 mCi/m^2 or half increments of 6.25 mCi/m^2, as determined by each prior cohort's tolerance of the study drug. Tolerability was determined according to a dose-escalation scheme based on dose-limiting toxicities (DLTs) and sub-DLTs. An evaluation of dose escalation occurred after all subjects in a cohort received the treatment dose and completed the 56-day post-treatment follow-up period. In general, anticipated toxicities related to treatment with ^{131}I-CLR1404 were considered criteria for the adjustment of dose escalation.

On day T6 after treatment dose administration, each subject had a ^{131}I whole body planar scan. A subset of patients with non-hepatic primary tumors at least 2 cm also had SPECT or SPECT/CT imaging performed on days T3, T6, T14, and T21. Their respective anatomical regions of interest were imaged on the GE Infinia SPECT/CT camera using a high-energy general purpose parallel-hole collimator with counts from the 15% energy window centered at 364 KeV. For assessment of ^{131}I-CLR1404 antitumor activity, all subjects had CT scans that were quantitated according to RECIST version 1.1 on day T56 and these were repeated every 2 months until disease progression or the start of another systemic therapy.

Tissue radiation doses estimates were calculated using image data from the ^{131}I-CLR1404 dosimetry phase. The provided biodistribution data were fit to simple exponential functions and the results of this analysis were used as in-

put to the OLINDA/EXM computer code for calculation of absorbed radiation doses (29, 30). Time integrals of activity were calculated and converted to numbers of disintegrations in the source organs; these values were entered into the OLINDA/EXM software using the adult male model. Elimination of the activity from the body was assumed to be solely through urinary excretion, using the dynamic bladder model in OLINDA/EXM, using a 3.5 hour bladder voiding interval.

Safety was assessed and PK samples were collected at scheduled time points throughout both phases of the study. For one year after day T56, subject follow-up continued at monthly intervals until initiation of new systemic therapy or death.

Assessments

Safety of ^{131}I-CLR1404 was assessed by adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examination, ECG readings, and ECOG performance status. Adverse events, graded on the basis of the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02, were assessed and recorded at each visit for the duration of the study. All study subjects who received study drug were included in the safety analysis.

To evaluate the PK profile of ^{131}I-CLR1404 in this population, plasma concentration versus time profiles were plotted in both linear and logarithmic scale for each subject, from which the following parameters were derived: area under the drug concentration curve (AUC); maximum plasma concentration (C_{max}); biologic half-life ($t_{1/2}$); plasma clearance (Cl); and volume of distribution (V_d).

All subjects who received the study drug during the treatment phase and had sufficient post-dosimetry PK sampling data available to calculate PK parameters were included in the PK analysis.

To assess antitumor activity of ^{131}I-CLR1404 in this population, subjects were followed with CT imaging at day T56 and every two months for one year or until disease progression or the start of another anti-cancer therapy. Variables examined included: best overall tumor response per RECIST 1.1 at trial closure, duration of response, time to response, and tumor markers as applicable.

RESULTS

Twelve patients were enrolled from December 2011 to November 2013. Two patients withdrew from study before receiving drug. A total of 10 patients received protocol therapy and their baseline patient characteristics are presented in Table 1. Each patient received an initial 5 mCi dose of ^{131}I-CLR1404 in the dosimetry phase. All 10 patients completed the dosimetry phase and continued on to complete the treatment phase. According to cohort assignment, each patient received a single dose of ^{131}I-CLR1404 based on BSA (BSA capped at 2.5 m^2) as follows: 2 subjects each at 12.5 mCi/m^2, 25 mCi/m^2 and 37.5 mCi/m^2. Four subjects received the de-escalated dose of 31.25 mCi/m^2.

Table 1. Patient demographic characteristics ($N = 10$)

Characteristic	N
Median age (years)	55 (Range 40–70)
Race	White: 9
	Asian: 1
Gender	Male: 5
	Female: 5
Tumor type	Colorectal: 3
	Breast: 2
	Prostate: 2
	Esophageal: 2
	Ovarian: 1
Previous lines of systemic cytotoxic therapy	3 lines: 6
	2 lines: 2
	1 line: 0
	0 lines: 2
ECOG PS	0: 6
	1: 4

Safety

The most common toxicities were hematologic (7 of 10 patients). DLTs related to treatment with ^{131}I-CLR1404 were Grade 4 neutropenia (2 of 2 patients at 37.5 mCi/m^2, 1 patient out of 4 at 31.25 mCi/m^2), and thrombocytopenia (1 of 2 patients at 37.5 mCi/m^2, 2 of 4 patients at 31.25 mCi/m^2). Neutropenia resolved within 2 weeks with growth factor support, and thrombocytopenia resolved spontaneously within 2 weeks. No DLTs were observed at either the 12.5 mCi/m^2 or 25 mCi/m^2 dose levels. Anemia was seen in 6 of 10 patients, most of which was attributed to the underlying malignancy. The majority of AEs (74%; 180 of 242) were considered to be mild or moderate (Grade 1 or 2) in intensity. A minority (29%; 70 of 242) of AEs were considered related to ^{131}I-CLR1404. Renal and hepatic functions were preserved in all patients as assessed by serum creatinine and liver enzyme tests. Adverse events are summarized in Table 2.

Response

Four of 10 treated subjects had a best overall response of stable disease at end-of-study (day T56). Patients with stable disease included 1 patient with ovarian cancer (received 31.25 mCi/m^2), 1 with triple-negative breast cancer (received 37.5 mCi/m^2), and 2 with castrate-resistant prostate cancer (received 12.5 and 25 mCi/m^2, respectively). At follow-up, 2 of these subjects, the patient with prostate cancer treated with 25 mCi/m^2 and the patient with triple-negative breast cancer, showed evidence of stable disease for 140 and 143 total days post-treatment, respectively.

Pharmacokinetics

After a single IV infusion of ^{131}I-CLR1404 during the treatment phase, plasma concentrations of CLR1404 generally declined in a biphasic manner, with the start of the apparent terminal elimination phase occurring around 144 hours (day T6) after the end of infusion. Mean Cl and Vd levels were roughly similar across dose levels, and Vd values were approximately 11–16% of the total body weight of a 70 kg person, indicating that ^{131}I-CLR1404 was moderately distributed

Table 2. Most common related adverse events from administered ^{131}I-CLR1404

Toxicity	Dosimetry 5 mCi/m^2 $N = 10$	12.5 mCi/m^2 $N = 2$	25 mCi/m^2 $N = 2$	31.25 mCi/m^2 $N = 4$	37.5 mCi/m^2 $N = 2$
Anemia	1 (10%)	0	1 (50%)	3 (75%)	2 (100%)
Neutropenia	0	0	1 (50%)	4 (100%)	2 (100%)
Thrombocytopenia	0	2 (100%)	2 (100%)	4 (100%)	2 (100%)
White blood cell count decreased	0	1 (50%)	2 (100%)	3 (75%)	2 (100%)
Bradycardia	0	0	1 (50%)	1 (25%)	0
QT prolonged	0	0	0	3 (75%)	0
Abdominal distention	0	0	1 (50%)	1 (25%)	0
Decreased appetite	0	0	1 (50%)	1 (25%)	0
Dyspnea	0	0	1 (50%)	0	1 (50%)
Fatigue	1 (10%)	2 (100%)	2 (100%)	2 (50%)	1 (50%)
Edema	0	0	2 (100%)	1 (25%)	0
Rash	0	0	0	1 (25%)	1 (50%)
Nail discoloration	0	0	1 (50%)	1 (25%)	0
Gamma-glutamyltransferase elevation	0	0	1 (50%)	0	2 (100%)

This table shows toxicities attributed to the study drug in more than 1 patient. Of 242 AEs recorded, 70, or 29% were considered at least possibly related to study drug. DLTs included Grade 4 neutropenia in 2 patients at 37.5 mCi/m^2, 1 at 31.25 mCi/m^2, and Grade 4 thrombocytopenia (1 at 37.5 mCi/m^2, 1 at 31.25 mCi/m^2). The majority of AEs (74%) were Grade 1–2 in severity. During dosimetry, no AEs exceeded Grade 2.

to extravascular tissues. The increases in mean C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ values were approximately dose-proportional between 12.5 and 31.25 mCi/m^2; however, the increase in dose from 31.25 to 37.5 mCi/m^2 did not result in increased C_{max} or AUC (Table 3). Pharmacokinetic data are shown in Figure 1.

The normal tissues with the highest absorbed doses were the spleen and myocardium (1.8 and 1.4 mSv/MBq). The effective dose was approximately 0.70 mSv/MBq. Coefficients of variation were under 15%, except for heart, kidneys, liver, lungs, and spleen (Table 4).

SPECT-CT imaging data showed selective ^{131}I-CLR1404 uptake and retention in a variety of tumor types and anatomic locations. For example, SPECT-CT was able to localize tumors in the hepatic parenchyma, and lung parenchyma (Figure 2); each of the assessed tumors had comparable ^{131}I-CLR1404 uptake.

DISCUSSION

This Phase 1 study of ^{131}I-CLR1404 conducted in patients with advanced disease demonstrated that single doses of ^{131}I-CLR1404 were tolerated without dose-limiting toxicities up to doses of 25 mCi/m^2. DLTs of neutropenia and thrombocytopenia were observed at doses of 31.25 mCi/m^2 and 37.5 mCi/m^2. Future disease-specific studies should be initiated at starting doses at or below a dose of 25 mCi/m^2.

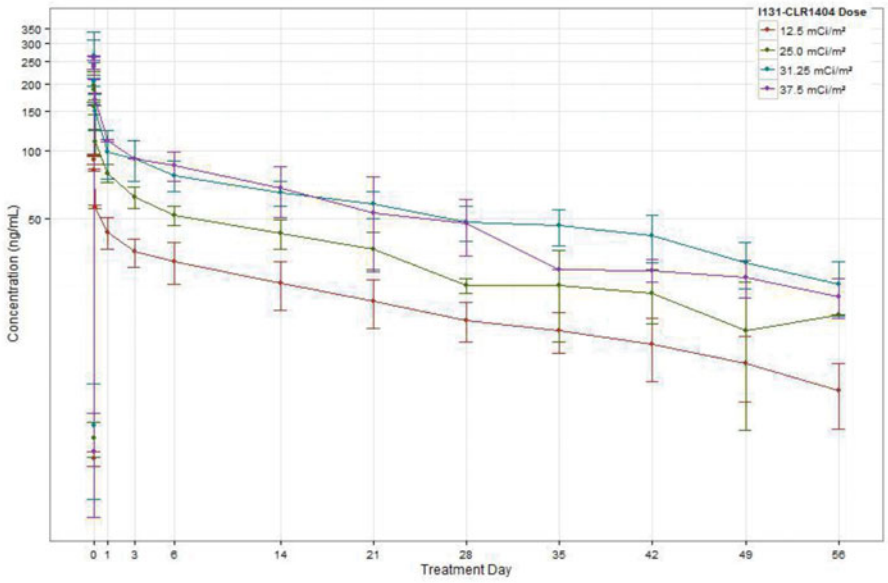

Figure 1. **Pharmacokinetic data, Concentration vs. Time (semilog):** Plasma concentrations of ^{131}I-CLR1404 declined in a biphasic manner, with the start of the apparent terminal elimination phase generally occurring circa 144 hours after the end of infusion. Mean $t_{1/2}$ values were similar across dose levels. Figure 1: Semilog PK Data.

Table 3. Mean (SD) Pharmacokinetic parameters for ^{131}I-CLR1404 following IV infusion during the treatment phase

PK parameter	12.5 mCi/m^2 $N = 2$	25 mCi/m^2 $N = 2$	31.25 mCi/m^2 $N = 4$	37.5 mCi/m^2 $N = 2$
C_{max} (ng/mL)	95.3 (NA)	196 (NA)	276 (68.2)	259 (NA)
$AUC_{0-\infty}$ (ng h/mL)	34000 (NA)	55900 (NA)	92100 (19100)	93100 (NA)
$t_{1/2}$ (h)	528 (NA)	555 (NA)	477 (121)	644 (NA)
Cl (mL/h)	12.1 (NA)	12.7 (NA)	11.8 (4.24)	12.0 (NA)
Vd (mL)	9270 (NA)	9940 (NA)	7860 (2150)	11300 (NA)

Mean Cl and Vd levels were roughly similar across dose levels, and Vd values were approximately 11–16% of the total body weight of a 70 kg person, indicating that ^{131}I-CLR1404 was moderately distributed to extravascular tissues. Mean increases in Cmax and AUC were dose proportional between 12.5 mCi/m^2 and 31.25 mCi/m^2 but further dose increase did not result in increased Cmax and AUC

Subject PK profiles demonstrated biphasic elimination patterns with a terminal elimination phase starting approximately 144 hours after infusion. Pharmacokinetic analyses demonstrated consistent $t_{1/2}$, Cl, and V_d across dose levels.

Imaging analysis of ^{131}I-CLR1404 showed selective tumor uptake and retention in multiple tumor types. Stable disease was demonstrated in four patients at end-of-study (Day T56). Duration of stable disease was up to 140 days after single infusions of study drug in two patients. All patients had progressive disease upon study entry. Although impacted by small patient numbers, achievement of stable disease was not obviously dose dependent, and occurred in different tumor types (breast and prostate).

This multi-institution study characterized the pharmacokinetic properties and toxicities of ^{131}I-CLR1404 in heavily pretreated patients using an adaptive dose-escalation scheme. Toxicities were self-limited and managed with standard supportive measures such as growth factor support. Limitations of the study include a small sample size and a heterogeneous population. In addition, the limitations of RECIST in response assessment for radiopharmaceuticals and radiotherapy in general have been described; true anticancer efficacy may be underestimated when RECIST endpoints are used (31). Similarly, SPECT-CT lacks sufficient resolution to reliably characterize response. We attempted to minimize that by preselecting patients with large-volume extrahepatic disease, but in doing so may have eliminated patients with smaller tumors who may benefit more from radiopharmaceuticals. In addition, while a reasonable standard for evaluation of intern al dose, OLINDA/EXM has shortcomings in terms of correlating calculated dose with clinically observed dose in radiopharmaceuticals. Particularly with marrow dose calculation, OLINDA/EXM may differ from MIRDOSE3 or other calculations. A more individualized platform could better characterize the specific dosimetry on a per-patient basis (30, 32). The heterogeneous patient population in terms of tumor types and prior treatments limits the estimation of clinical efficacy. Future studies will be focused on specific tumor

Table 4. **Radiation dose estimates:** The fraction of injected activity of ^{131}I-CLR1404 was calculated by OLINDA/EXM

	Average		Std Dev		
	mSv/MBq	rem/mCi	mSv/MBq	rem/mCi	COV %
Adrenals	0.717	2.65	0.0891	0.329	12.4
Brain	0.571	2.11	0.0827	0.306	14.5
Breasts	0.553	2.05	0.0770	0.286	13.9
Gallbladder Wall	0.736	2.72	0.0858	0.319	11.7
LLI Wall	0.697	2.58	0.0999	0.369	14.3
Small Intestine	0.714	2.64	0.0987	0.365	13.8
Stomach Wall	0.695	2.57	0.0937	0.346	13.5
ULI Wall	0.705	2.61	0.0954	0.353	13.5
Heart Wall	1.430	5.30	0.479	1.77	33.5
Kidneys	0.820	3.03	0.426	1.57	52.0
Liver	0.874	3.24	0.294	1.09	33.6
Lungs	0.864	3.19	0.307	1.13	35.6
Muscle	0.614	2.27	0.0855	0.317	13.9
Ovaries	0.716	2.65	0.102	0.376	14.2
Pancreas	0.753	2.79	0.0962	0.356	12.8
Red Marrow	0.550	2.04	0.0755	0.279	13.7
Osteogenic Cells	1.260	4.65	0.178	0.662	14.2
Skin	0.519	1.92	0.0734	0.271	14.1
Spleen	1.770	6.54	0.739	2.74	41.8
Testes	0.604	2.23	0.0873	0.324	14.4
Thymus	0.671	2.48	0.0934	0.347	13.9
Thyroid	0.635	2.35	0.0915	0.340	14.4
Urinary Bladder Wall	0.715	2.65	0.0500	0.185	70.0
Uterus	0.719	2.66	0.102	0.379	14.2
Total Body	0.647	2.40	0.0848	0.312	13.1
Effective Dose	0.697	2.58	0.0981	0.364	14.1

Values were highest in spleen and myocardium, and the total body effective dose was 0.7mSv/MBq

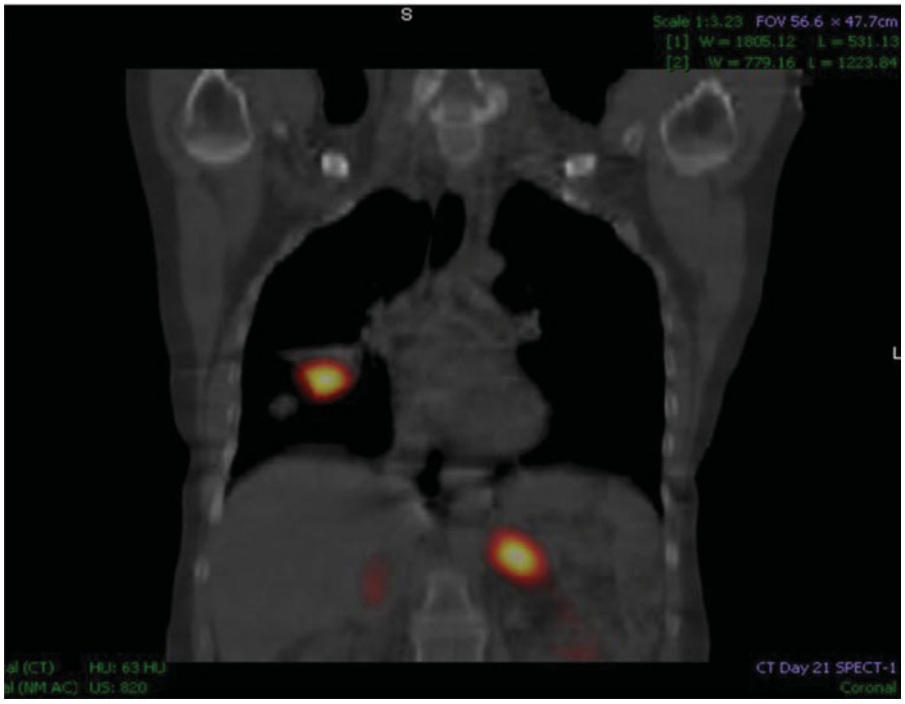

Figure 2. SPECT-CT fused images from a patient (100107) with lung and nodal metastases from colon cancer. Day 21 postinfusion coronal SPECT-CT demonstrating selective uptake of ^{131}I-CLR1404 in known metastatic foci of a patient with colorectal cancer. Tumor signal was retained beyond 21 days (images not shown).

types with specific prior treatments to better assess efficacy and toxicity.

The imaging data demonstrated that CLR1404 has exquisite tumor sensitivity for both primary tumors and sites of metastatic disease. The radiotracer showed increased uptake relative to background organs a variety of anatomic sites (e.g. pleura, lung, nodal deposits; see images). Evidence of uptake of the compound was seen at the last SPECT imaging time point, which was 21 days post administration, with little to no retention in normal tissues. Studies are underway to assess the potential of different iodine radioisotopes coupled to CLR1404 as potential therapeutic and diagnostic (imaging) agents. In addition, fluorophores have been attached to CLR1404, and these agents have retained the tumor-targeting characteristics of CLR1404 and may prove useful for fluorescence-guided surgery (33, 34).

The dose-dependent, predictable, reversible neutropenia and thrombocytopenia merit further exploration. The timing was consistent in each patient; the decline in platelets began predictably by day 21, and was most pronounced day 35–42. All patients began to see recovery by day 56. The same timing was observed for neutrophils, suggesting a cytotoxic effect from radiation. We hypothesize that although selective tumor uptake and retention is observed, the protracted plasma half-life of CLR1404 results in significant radiation exposure to circulating blood cells and precursors. The timing, severity, and duration of these toxicities are similar to those seen in other radiopharmaceuticals, suggesting that these side effects are a direct result of the radioisotope, rather than the PLE delivery mechanism, which has demonstrated safety in preclinical and clinical trials (35). Further testing to identify and minimize this toxicity will be critical in optimizing the safety profile of this compound. Future clinical trials of ^{131}I-CLR1404 are ongoing in radiosensitive malignancies.

DECLARATION OF INTEREST

No conflict for Lubner, Mullvain, Perlman, Pishvaian, Mortimer, Heideman, and Liu. Oliver: Employee of Cellectar Biosciences, Inc. Weichert: Founder, Director and Chief Scientific Officer of Cellectar Biosciences. The authors alone are responsible for the content and writing of the article.

FINANCIAL SUPPORT

Study funded by Cellectar Biosciences, Inc.

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