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Original Article

Phase 1 Study of No-Carrier Added ^{177}Lu-DOTATATE (SNU-KB-01) in Patients with Somatostatin Receptor–Positive Neuroendocrine Tumors: The First Clinical Trial of Peptide Receptor Radionuclide Therapy in Korea

Hyun Gee Ryoo[1,2], **Minseok Suh**[1], **Keon Wook Kang**[1,3,4], **Dae-Won Lee**[5], **Sae-Won Han**[5], **Gi Jeong Cheon**[1,3,4]

[1]Department of Nuclear Medicine, Seoul National University Hospital, Seoul, [2]Department of Nuclear Medicine, Seoul National University Bundang Hospital, Seongnam, [3]Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, [4]Cancer Research Institute, Seoul National University, Seoul, [5]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Purpose To provide a wider choice of treatment opportunities for patients with neuroendocrine tumor (NET) in Korea, we have conducted a phase 1, open-label, single-arm, dose-escalation study of SNU-KB-01, a no-carrier added (NCA) ^{177}Lu-labeled DOTATATE.

Materials and Methods Seven patients with inoperable, progressive, metastatic, or locally advanced, somatostatin receptor-positive NET with Ki67 index ≤ 20% were enrolled according to the rolling six design. The study consisted of two cohorts to receive 4 cycles of SNU-KB-01 every 8 weeks for the first dose of 5.55 GBq (n=3) and 7.40 GBq (n=4). We assessed the incidence of dose-limiting toxicity (DLT) and adverse event, absorbed dose of kidneys and bone marrow, and objective tumor response.

Results Seven patients completed 4 cycles (21.3-30.1 GBq total dose) of SNU-KB-01. The mean absorbed doses to kidneys and bone marrow were 0.500 mGy/MBq and 0.053 mGy/MBq, respectively, and the total body effective dose was 0.115 mSv/MBq. No DLT was observed and the maximum tolerated dose was 7.40 GBq/cycle. Grade 3 thrombocytopenia occurred in one patient, but no other grade 3 or 4 major hematologic or renal toxicity was observed. The best objective response to SNU-KB-01 was partial response. Overall response rate was 42.9% and disease control rate was 85.7%.

Conclusion Treatment with 4 cycles of SNU-KB-01 was well tolerated and resulted in control of disease in most of the patients. Our results indicate SNU-KB-01, an NCA ^{177}Lu-labeled DOTATATE, as a potentially safe and efficacious treatment option for NET patients in Korea.

Key words SNU-KB-01, ^{177}Lu-DOTATATE, No-carrier added, Neuroendocrine tumors, Peptide receptor radionuclide therapy

Introduction

Neuroendocrine tumors (NETs) are heterogeneous groups of neoplasm arising from neuroendocrine cells in various anatomical locations throughout the body [1,2]. NET generally has indolent nature, but it could behave aggressively at the advanced stage with multiple distant metastases which requires systemic therapies. Since most NETs overexpress somatostatin receptor (SSTR) [3], peptide receptor radionuclide therapy (PRRT) with somatostatin analog has been introduced in the treatment of NETs over the last decades [4-8].

Even though ^{177}Lu-DOTATATE (Lutathera, Advanced Accelerator Applications) was approved for the treatment of somatostatin-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in the United States in 2018 [9], NET patients in Korea had limited access to the treatment until it was approved in Korea in 2020. Even after 2020, NET patients in Korea still have limited opportunities for PRRT due to its restricted indication and high cost. Moreover, patients with various types of SSTR-positive NETs other than GEP-NET have little chance of PRRT due to its restricted indication.

Inspired by the recent situation in Korea, we conducted a phase 1 clinical trial of SNU-KB-01, a no-carrier added (NCA) ^{177}Lu-DOTATATE, to provide a wider choice of treatment opportunities for NET patients in Korea. We investigated the safety, tolerability, dosimetry, and exploratory efficacy of SNU-KB-01 in patients with SSTR-positive NETs.

Materials and Methods

1. Patient selection

This is an open-label, single-arm, dose-escalation, phase 1 clinical trial to evaluate the safety, tolerability, and dosimetry of the investigational drug SNU-KB-01. This was an investigator-initiated, single-institution study conducted in Korea

Correspondence: Gi Jeong Cheon
Department of Nuclear Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: 82-2-2072-3386 Fax: 82-2-745-7690 E-mail: larrycheon@gmail.com
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from March 2020 to April 2021.

Pathologically proven NET patients were prospectively enrolled between March 2020 and August 2020. The eligibility criteria included inoperable, progressive under previous therapy, metastatic or locally advanced NET of any origin with Ki67 index ≤ 20% and positive-SSTR scan. Positive-SSTR scan was defined as a tumor uptake greater than or equal to the normal liver uptake (i.e., Krenning score of 2 and above) on ^{68}Ga-DOTATOC positron emission tomography (PET)/computed tomography (CT). The patients with the marked impairment in the kidney (serum creatinine greater than 1.7 mg/dL or creatinine clearance less than 50 mL/min), bone marrow (hemoglobin concentration less than 8.0 g/dL; white blood cell [WBC] count less than 2,000/μL; platelet count less than 75,000/μL), and liver (total bilirubin greater than 3× upper limit of normal; serum albumin less than 3.0 g/dL and prothrombin time [international normalized ratio] greater than 1.5) were excluded from the study. The detailed inclusion and exclusion criteria for this clinical trial are given in S1 Table.

2. Study design and PRRT protocol

The study consisted of two cohorts (maximum 6 patients per cohort) for the first dose levels of SNU-KB-01 (5.55 GBq and 7.40 GBq) to receive 4 cycles of PRRT. The study used a rolling six design for the enrollment and dose-escalation of SNU-KB-01 to identify the maximum tolerated dose (MTD). The rolling six design was used when the dose and toxicity of the drug were already known in one population and were to be tested in another population [10]. We employed this method to minimize delays in the dose-escalation phase and shorten the duration of the study. We could introduce a rolling six design in SNU-KB-01 because the dose and toxicity profile of ^{177}Lu-DOTATATE was already reported in a previous study of Lutathera [9], and radiation toxicity can be expected from the administered dose since the absorbed dose limit of the dose-limiting organ was already established [11,12]. The starting dose was 5.55 GBq for the first cycle with a planned escalation to 7.40 GBq in a subsequent cohort when the dose-escalation criteria are met: 3/3, 4/4, 5/5, 5/6, or 6/6 patients in the 5.55 GBq dose cohort are evaluated without dose-limiting toxicity (DLT) (Fig. 1). Patients in the 5.55 GBq dose cohort could have dose-escalation to 7.40 GBq in subsequent cycles when 3/3, 4/4, 5/5, 5/6, or 6/6 patients in the 7.40 GBq dose cohort are evaluated without DLT.

SNU-KB-01, an NCA ^{177}Lu-DOTATATE, was manufactured by KaiBioTech (Jeonju, Korea), and analytical and quality assurance testing was performed before the administration to the patients. Patients were planned to receive 4 cycles of SNU-KB-01 every 8 weeks. In each cycle, SNU-KB-01 was intravenously administered by syringe infusion pump over 30 minutes. Antiemetic premedication (8 mg ondansetron dissolved in normal saline) and kidney protecting agent were intravenously administered 1 hour and 30 minutes prior to SNU-KB-01 respectively. Kidney protecting agents, a 2,000 mL solution (Glamin, Fresenius Kabi Korea, Seoul, Korea) composed of a mixture of amino acids, and a 1,000 mL normal saline were continued for 4 to 6 hours.

3. Safety assessment

Any adverse events after PRRT were recorded after each cycle. Physical examination and laboratory tests (blood counts, liver, and kidney biochemistry) were performed prior to and 2, 4, 6, and 8 weeks after the first cycle, and 4

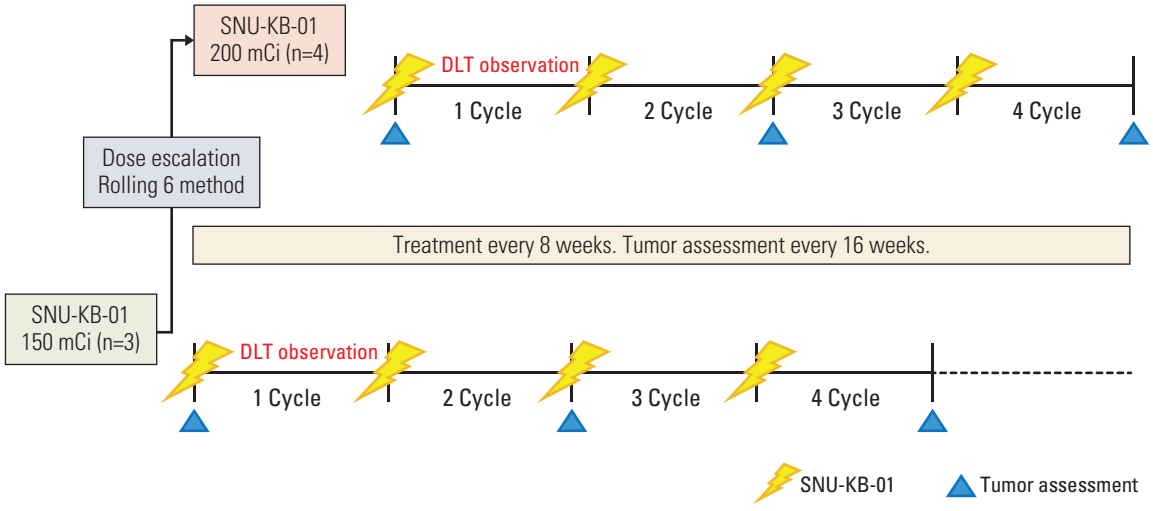

Fig. 1. Study design of peptide receptor radionuclide therapy with SNU-KB-01. DLT, dose-limiting toxicity.

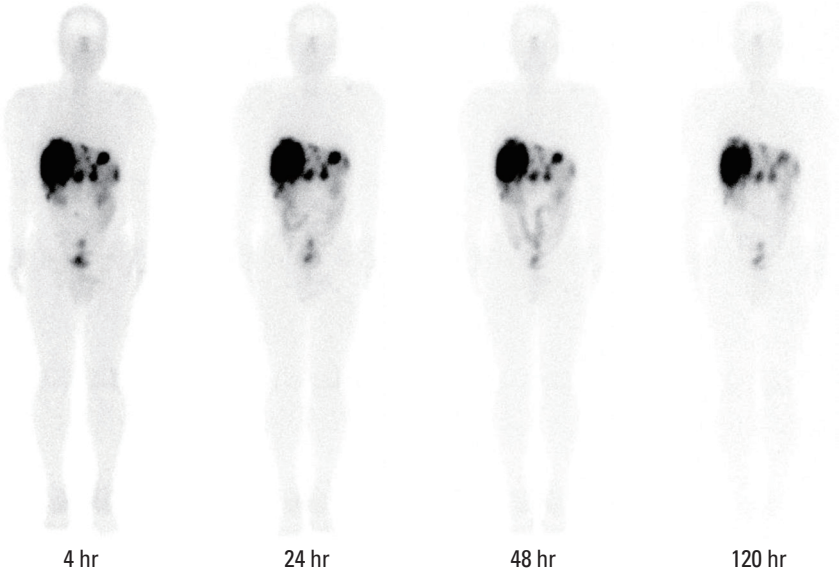

Fig. 2. Representative ^{177}Lu-DOTATATE whole-body planar scans of a patient with rectal neuroendocrine tumor with multiple metastases in liver, lymph nodes, bones at 4, 24, 48, and 120 hours after administration of SNU-KB-01.

and 8 weeks after the subsequent cycles. DLT was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events ver. 5.0 (CTCAE), and it is defined as an adverse drug reaction that is any of the following toxicities in S1 Table. The DLT observation period was 8 weeks after the first administration of SNU-KB-01, and the frequency of DLT during the observation period was evaluated for the determination of MTD. Dose reduction and treatment delay were considered when dose-limiting or dose-modifying toxicity occurred.

4. Dosimetry

^{177}Lu-DOTATATE whole-body planar scans and single photon emission computed tomography (SPECT)/CT were performed approximately 4, 24, 48, and 120 hours after the administration of SNU-KB-01 using a dedicated hybrid SPECT/CT scanner (Discovery NM/CT 670, GE Healthcare, Milwaukee, WI) with a medium-energy general-purpose collimator and a 20% energy window width centered symmetrically over the 208-keV photopeak of ^{177}Lu (Fig. 2). The whole-body images were acquired on a dual-headed planar imaging with 1,024×256 matrices at a scan speed of 18 cm/min. SPECT/CT images covering at least the liver and kidneys were acquired in step and shoot mode, 120 projections (60 per detector head), 20 seconds per projection, and matrix size 128×128. Images were reconstructed using an iterative algorithm (ordered subset expectation maximization, iteration 2, subset 10), and CT images were reconstructed into a 3.75-mm-thick slice.

Dosimetric analysis was performed in three patients after administration of 5.55 GBq of SNU-KB-01 for the first cycle of PRRT. Radiation dosimetry was performed based on the Medical Internal Radiation Dose (MIRD) S-value methodology. Kidneys, liver, spleen, and bone marrow were selected as source organs. Using MIM software (MIM EncoreTM, MIM Software Inc., Cleveland, OH), images were evaluated at each time point. The radiotracer activity was quantified as percentage injected dose (%ID), and the time-activity curve was plotted for each source organ. The radioactivity in the remainder of the body was defined as the value obtained by subtracting the source organ activity and tumor uptake from the whole-body activity. A reference source with a known activity was prepared and measured, using the same acquisition protocol, for the conversion of the count per minute to activity. For each source organ and remainder of the body, mono-exponential or bi-exponential functions were iteratively fitted to the time-activity curve and subsequent residence time was calculated using OLINDA/EXM, ver. 1.1. The absorbed dose of various organs and total body effective dose was estimated by entering the residence time of the source organs and the remainder of the body.

5. Efficacy assessment

The extent of disease and tumor response to PRRT was assessed by contrast-enhanced CT or magnetic resonance imaging and ^{68}Ga-DOTATOC PET/CT at baseline and 8 weeks after the second and fourth cycles of PRRT. Objective tumor response was evaluated according to Response

Table 1. Patient, tumor, and treatment characteristics

Patient No.	Age (yr)	Sex	Primary tumor (Ki67, %)	Metastases	Previous treatments	Tumor burden	Krenning score	Treatment cycles	Cumulative dose (GBq)
1	52	M	Rectum (5.0)	Liver, bone, lymph nodes	Lanreotide	Extensive	4	4	24.0
2	59	M	Pancreas (5.8)	Liver, bone, lymph nodes	TACE, everolimus, sunitinib	Extensive	4	4	24.8
3	53	M	Rectum (5.0)	Liver, bone, lymph nodes	Lanreotide, everolimus, radiotherapy	Extensive	4	4	21.3
4[a]	41	M	Pancreas (1.0), thymus (10.0)	Liver, bone, lymph nodes, adrenal gland	Etoposide and cisplatin[b], radiotherapy, everolimus, sunitinib, lanreotide	Extensive	3	4	30.0
5	63	M	Rectum (7.0)	Liver, bone, lymph nodes, diaphragm, peritoneum	TACE, everolimus	Extensive	4	4	28.9
6	74	M	Rectum (7.5)	Liver, bone	TACE	Moderate	4	4	30.0
7	69	M	Rectum (14.4)	Liver	TACE, lanreotide	Moderate	3	4	30.1

TACE, transarterial chemoembolization. [a]Patient with multiple endocrine neoplasia type 1, [b]Treatment for thymic neuroendocrine tumor.

Evaluation Criteria in Solid Tumors (RECIST ver. 1.1). When progressive disease (PD) is confirmed according to RECIST criteria during the treatment, the administration of SNU-KB-01 for the individual patient was planned to be discontinued. The overall response rate (ORR) was defined as the proportion of patients who have a complete response (CR) or partial response (PR), and the disease control rate (DCR) as the proportion of patients who have CR, PR, or stable disease (SD) 8 weeks after the last administration of SNU-KB-01 of the individual patient. The extent of tumor burden score was determined by assessing the number of SSTR-positive tumors on ^{68}Ga-DOTATOC PET/CT: extensive, many tumor sites in ≥ 2 parts of the body (head/neck, chest, upper abdomen, lower abdomen); moderate, multiple metastatic lesions in up to two parts of the body; limited, up to five sites in one part of the body.

6. Data analysis

The primary endpoints of this study included safety, tolerability, and determination of MTD/recommended phase 2 dose. Secondary endpoints included dosimetry and efficacy. Continuous variables were presented as mean with standard deviation, and categorical data were given as frequencies and percentages for statistical analysis. The progression-free survival (PFS) and overall survival (OS) were measured from the date of the first administration of SNU-KB-01 and were analyzed using the Kaplan-Meier method.

Results

1. Patient characteristics

Seven patients with grade 1 and grade 2 SSTR-positive inoperable, progressive, metastatic, or locally advanced NET completed 4 cycles of treatment with SNU-KB-01 between April 2020 and February 2021. Three patients were initially enrolled in the 5.55 GBq dose cohort and four patients in the 7.40 GBq dose cohort. Patient demographics and tumor characteristics are summarized in Table 1. The mean age was 58.7±11.2 years and all participants were male. The primary tumor site included the rectum (5/7), pancreas (1/7), and both pancreas and thymus (1/7) in a patient with multiple endocrine neoplasia type 1 (MEN1). Most patients presented with metastases in the liver (7/7), bone (6/7), lymph node (5/7), and metastases in the adrenal gland, diaphragm, and peritoneum existed in one patient respectively. All patients were progressive under previous therapy. The extent of tumor burden score was extensive in five patients and moderate in two patients. Patients received PRRT with an average dose of 6.75 GBq (range, 4.32 to 8.07 GBq) per cycle, and the average cumulative dose after completion of 4 cycles of

Table 2. Hematologic, biochemical toxicity, and clinical adverse events

	Per cycle (n=28)				Per patient (n=7)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic and biochemical toxicity								
Hemoglobin	7 (25.0)	1 (3.6)	0	0	1 (14.3)	1 (14.3)	0	0
Platelet	5 (17.9)	2 (7.1)	1 (3.6)	0	4 (57.1)	0	1 (14.3)	0
WBC	7 (25.0)	6 (21.4)	0	0	1 (14.3)	4 (57.1)	0	0
ANC	4 (14.3)	1 (3.6)	0	0	2 (28.6)	1 (14.3)	0	0
Creatinine	0	0	0	0	0	0	0	0
GFR	1 (3.6)	0	0	0	1 (14.3)	0	0	0
AST	2 (7.1)	0	0	0	1 (14.3)	0	0	0
ALT	0	0	0	0	0	0	0	0
Total bilirubin	3 (10.7)	1 (3.6)	0	0	0	1 (14.3)	0	0
Clinical adverse events								
Diarrhea	1 (3.6)	1 (3.6)	0	0	1 (14.3)	1 (14.3)	0	0
Nausea	5 (17.9)	0	0	0	5 (71.4)	0	0	0
Vomiting	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Chest discomfort	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Chest pain	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Extravasation	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Fever	2 (7.1)	0	0	0	2 (28.6)	0	0	0
Liver abscess	0	0	1 (3.6)	0	0	0	1 (14.3)	0
URI	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Anorexia	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Arthralgia	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Dizziness	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Pleural effusion	1 (3.6)	0	0	0	1 (14.3)	0	0	0
Alopecia	3 (10.7)	0	0	0	2 (28.6)	0	0	0
Sweating	2 (7.1)	0	0	0	1 (14.3)	0	0	0
Urticaria	1 (3.6)	0	0	0	1 (14.3)	0	0	0

Values are presented as number (%). ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; GFR, glomerular filtration rate; URI, upper respiratory infection; WBC, white blood cell.

SNU-KB-01 was 27.0 GBq (range, 21.3 to 30.1 GBq) per patient.

2. Toxicity

All patients received 4 cycles of SNU-KB-01 without any DLT, and MTD was 7.40 GBq/cycle. One patient in the 5.55 GBq dose cohort postponed the second and fourth cycles due to grade 2 thrombocytopenia, respectively. The administered dose for the second cycle dose was also reduced to 4.32 GBq for this patient. Hematological, renal, and hepatotoxicity of SNU-KB-01 are presented in Table 2. There was grade 3 thrombocytopenia in one patient (14.3%), but no other grade 3 or 4 major hematologic, renal, hepatotoxicity was observed. Grade 1 or 2 hematologic toxicities were anemia (28.6%), thrombocytopenia (57.1%), leukopenia (71.4%), and neutropenia (42.9%). Grade 1 renal toxicity occurred in one patient (14.3%). Grade 1 or 2 hepatotoxicities were observed in two patients (28.6%). The trend of the progressive decline of hematological parameters was observed during the treatment cycles (Fig. 3).

Any clinical adverse events reported during the treatment cycles are summarized in Table 2. Adverse events which are considered to be related to SNU-KB-01 were grade 1 alopecia, nausea, and extravasation. Liver abscess was a serious adverse event that occurred during the treatment cycle in one patient, but it was classified as unrelated to SNU-KB-01 since the patient had recurrent liver abscess as a pre-existing condition. Nausea was the most common adverse event which is more likely to be a side effect of amino acid infusion. All clinical adverse events reported in Table 2 were resolved.

3. Dosimetry

The mean absorbed dose for each organ and the mean total body effective dose are summarized in Table 3. The organ with the highest absorbed dose was the kidney with

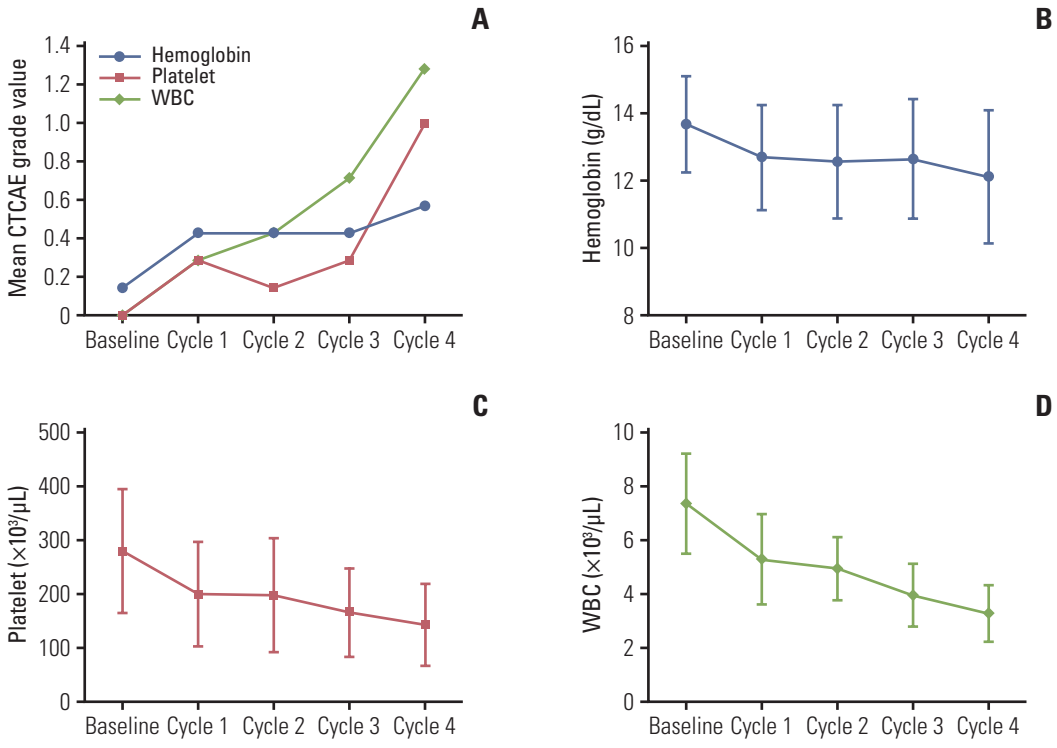

Fig. 3. Changing trend of mean Common Terminology Criteria for Adverse Events (CTCAE) grade value (A), hemoglobin (B), platelet (C), white blood cell (WBC) counts (D) for hematologic toxicity after cycles of SNU-KB-01. The trend of the progressive decline of hematological parameters was observed during the treatment cycles.

0.500 mGy/MBq, followed by the spleen with 0.177 mGy/MBq. The average absorbed dose to the bone marrow was 0.053 mGy/MBq. At an activity administration schedule of 4 cycles of 7.40 GBq, the cumulative absorbed doses to kidneys and bone marrow are calculated to be 14.8 Gy and 1.57 Gy, respectively. The mean total body effective dose was 0.115 mSv/MBq. Individual patient dosimetry data is available in S2 Table.

4. Efficacy

Among seven patients, the best objective response to SNU-KB-01 was the PR observed in three patients (42.9%) (Figs. 4 and 5). No CR was observed. Three patients (42.9%) had SD and one patient (14.3%) had PD. The ORR (CR+PR) was 42.9%, and the DCR (CR+PR+SD) was 85.7% (Table 4). In addition, two patients had a further decrease in the size of tumors 6 months after the fourth cycle of PRRT: patient 2 showed radiologic SD after the fourth cycle but had PR on a 6-month follow-up. With a median follow-up of 7.8 months, the PFS rates at 3 months, 6 months, and 9 months were 100%, 100%, and 75.0% (95% confidence interval, 12.8 to 96.1), respectively (Fig. 6). No patients died during the follow-up. The median PFS and OS have not been reached yet.

Discussion

For the first time in Korea, we conducted a phase 1 clinical trial of PRRT with SNU-KB-01 in patients with NET. Treatment with 4 cycles of SNU-KB-01 was well tolerated and resulted in disease control in most patients indicating the safety and efficacy of SNU-KB-01.

Our preliminary efficacy results of SNU-KB-01, an NCA ^{177}Lu-DOTATATE, in the treatment of patients with SSTR-positive NETs are encouraging. In our study, 85.7% of patients had disease control (3 PR and 3 SD) and only one patient showed progression. While we acknowledge that the sample size of our phase 1 study is limited, our results are comparable to or may have a better response rate than previous studies [7,9,13]. The only patient with PD (with MEN1) had the lowest tumor uptake on ^{68}Ga-DOTATOC PET and ^{177}Lu-DOTATATE scan among enrolled patients: most of the tumors in this patient had relatively low SSTR expression (equal to normal liver uptake) and only a single hepatic metastasis showed the highest uptake of Krenning score 3. The tumor absorbed dose of this patient (with PD) is expected to be lower compared to other patients (with disease control) who had higher tumor uptake at least above liver uptake in

Table 3. Summary of dosimetry data

Organs	Mean absorbed dose (mGy/MBq)
Adrenals	0.035
Brain	0.029
Breasts	0.030
Gallbladder wall	0.053
Lower large intestine wall	0.030
Small intestine	0.033
Stomach wall	0.034
Upper large intestine wall	0.035
Heart wall	0.036
Kidneys	0.500
Liver	N/A[a]
Lungs	0.035
Muscle	0.031
Pancreas	0.063
Red marrow	0.053
Osteogenic cells	N/A[a]
Skin	0.050
Spleen	0.177
Testes	0.050
Thymus	0.053
Thyroid	0.051
Urinary bladder wall	0.052
Total body effective dose (mSv/MBq)	0.115

[a]Liver and osteogenic cell dosimetry was hampered by the presence of extensive metastases, which are inherent to the clinical status of the enrolled patients.

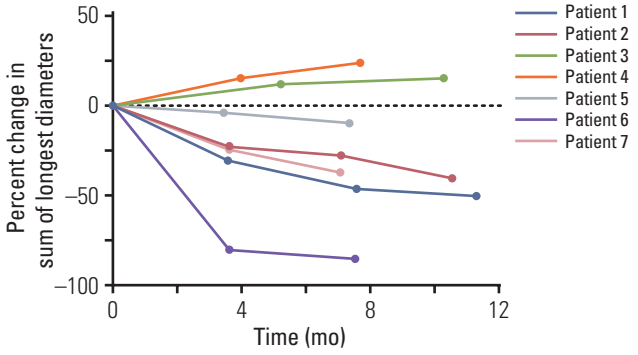

Fig. 4. Percent changes in the sum of diameters of target lesions from baseline during peptide receptor radionuclide therapy with SNU-KB-01.

most of their tumors. The late radiological response of the tumor for delayed radiation effect also should be considered for the response evaluation after PRRT. In addition, patients with the second and third lowest tumor responses received suboptimal doses due to the bone marrow toxicity (patient 3) and the radioisotope delivery issue (patient 5). Thus, administration of an optimal dose of SNU-KB-01 in patients with high SSTR expression is expected to be a promising method for the treatment of NET.

In this study, SNU-KB-01 was synthesized using an NCA ^{177}Lu. Theoretically, NCA ^{177}Lu does not contain metastable ^{177m}Lu to yield maximum specific activity. Achievement of the highest specific activity is important in the targeted

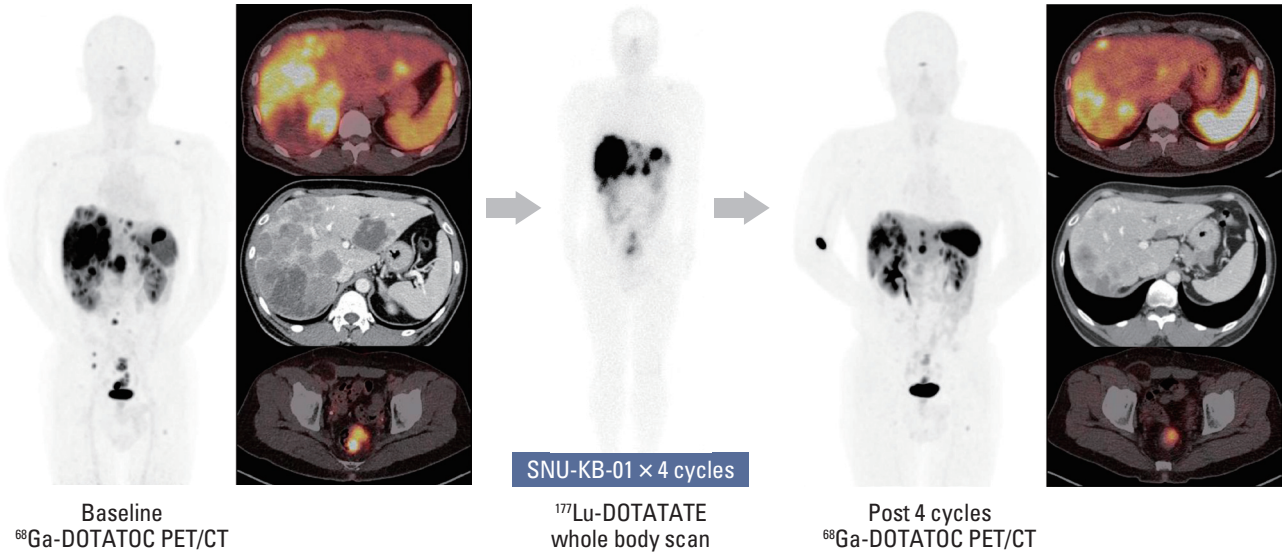

Fig. 5. ^{68}Ga-DOTATOC positron emission tomography (PET)/computed tomography (CT), contrast-enhanced liver CT, and ^{177}Lu-DOTATATE whole-body planar scan in a 52-year-old man with rectal neuroendocrine tumor and multiple metastases in liver, lymph nodes, and bones. He had a partial response (–46.3%) after the treatment with four cycles of SNU-KB-01.

Table 4. Objective tumor responses after four cycles of SNU-KB-01

Response category	No. (%) (n=7)
Objective response rate	3 (42.9)
Disease control rate	6 (85.7)
Complete response	0
Partial response	3 (42.9)
Stable disease	3 (42.9)
Progressive disease	1 (14.3)

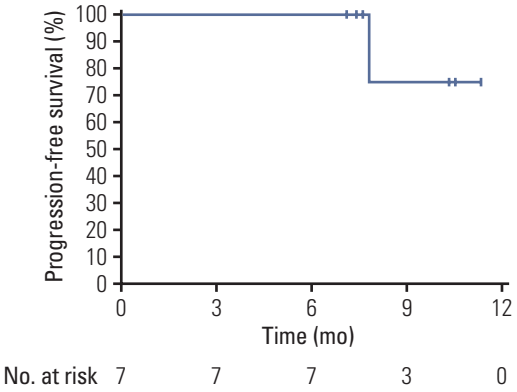

Fig. 6. Kaplan-Meier curve of progression-free survival after the first cycle of SNU-KB-01.

radionuclide therapy, especially when it is applied for the treatment of the target with low capacity. Targeting SSTR in tumors for radiolabeled peptide analogs are low-capacity systems, and high specific activity is necessary for the effective treatment [14]. In the study comparing NCA and carrier-added (CA) ^{123}I-MIBG for the assessment of cardiac sympathetic nerve activity, NCA ^{123}I-MIBG yielded a higher myocardial uptake and retention than CA ^{123}I-MIBG but did not result in a major difference in estimated absorbed dose [15]. In the study with a cohort of patients treated with NCA ^{177}Lu-DOTATATE as first-line therapy and consecutively with CA ^{177}Lu-DOTATATE after their relapse, calculated absorbed doses were higher in tumors but lower in blood and kidneys in NCA than CA ^{177}Lu-DOTATATE [16]. From these findings, SNU-KB-01, an NCA ^{177}Lu-DOTATATE can be reasonably inferred to have higher uptake to SSTR-positive tumors with no significant difference in absorbed dose and toxicities.

The estimated cumulative absorbed dose to bone marrow for 4 cycles of 7.40 GBq SNU-KB-01 (1.57 Gy) was similar to Lutathera European Medicines Agency report (1.5±1.1 Gy) [17], and did not reach the recommended dose limit of 2 Gy to minimize possible bone marrow complications [11]. The estimated absorbed dose of SNU-KB-01 to the kidneys also did not reach the limit of 23 Gy, which is the absorbed dose limit used for the conventional external beam radiotherapy [12]. Furthermore, considering the low-dose rate in PRRT, a higher absorbed dose can be accepted. Within the dose range set by the recommended dose per cycle of SNU-KB-01, it is expected that there will be no significant risk of human toxicity from radiopharmaceutical administration.

Treatment with SNU-KB-01 was well tolerated with an acceptable hematological, renal, and hepatotoxicity profile. Toxicity in the kidney and liver was very rare without any major grade 3 or 4 toxicity. Grade 1 or 2 hematologic toxicity more often occurred during the treatment, and grade 3 thrombocytopenia was reported in one patient. Decreases in WBC and platelet counts were more frequently observed in the later cycle (Fig. 3) which must be watched carefully during the treatment, especially in the later cycle of PRRT. Hemoglobin was less affected since it has relatively lower radiosensitivity and slower regeneration time [18,19].

The approved indication of ^{177}Lu-DOTATATE is confined to the treatment of patients with SSTR-positive GEP-NET so far [9]. However, many previous studies with ^{177}Lu-DOTATATE showed effective treatment responses to other types of SSTR-positive tumors, such as pheochromocytoma and paraganglioma [20], neuroblastoma [21], meningioma [22], medullary thyroid carcinoma [23], lung NETs [24], and pituitary tumor [25]. To provide treatment opportunities to the patients with various types of NETs who do not have any other treatment option, SNU-KB-01 has been used as a compassionate drug for treating a few patients with neuroblastoma, pheochromocytoma, and paraganglioma in Korea. Even though our study did not include patients with NET other than GEP-NET, we expect SNU-KB-01 could expand the indication for the treatment of various types of SSTR-positive tumors in the future.

The limitation of this study is the small number of participants and the short duration of follow-up. A phase 2 trial with a large number of patients is warranted to establish the efficacy of SNU-KB-01 on SSTR-positive NET. A limitation of dosimetry analysis is that the MIRD S-value methodology used by Olinda/EXM cannot define the S-value of the tumor to normal organs, so it cannot reflect the cross-fire effect caused by the adjacent tumor. Although ^{177}Lu mostly emits beta-rays with a short-range, it can have a non-negligible effect depending on the tumor burden. Considering these points, the absorbed dose of organs measured in this study can be underestimated. Future studies with voxel-based dosimetry are warranted for the accurate estimation of absorbed dose in normal organs [26].

In conclusion, for the first time in Korea, we have conducted a clinical trial of PRRT with SNU-KB-01, a NCA ^{177}Lu-DOTATATE, in patients with SSTR-positive NET. Treatment with SNU-KB-01 was safe and resulted in control of disease

in most of the patients with high SSTR expression. The recommended dose per cycle of SNU-KB-01 was determined to be 7.40 GBq for the phase 2 trial. Our results indicate SNU-KB-01 as a potentially safe and efficacious treatment option for NET patients and are expected to provide a wider choice of treatment opportunities for patients with various types of SSTR-positive tumors in Korea.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Ministry of Food and Drug Safety in Korea and the institutional review board of the Seoul National University Hospital (IRB No. 1912-071-1088). This trial was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice. Written informed consent was obtained from all participants.

Author Contributions

Conceived and designed the analysis: Ryoo HG, Suh M, Cheon GJ.
Collected the data: Ryoo HG, Suh M, Cheon GJ.
Contributed data or analysis tools: Ryoo HG, Suh M, Kang KW, Lee DW, Han SW, Cheon GJ.
Performed the analysis: Ryoo HG, Suh M, Cheon GJ.
Wrote the paper: Ryoo HG, Suh M, Cheon GJ.

ORCID iDs

Hyun Gee Ryoo : https://orcid.org/0000-0001-5020-5846
Gi Jeong Cheon : https://orcid.org/0000-0002-1360-5186

Conflicts of Interest

SNU-KB-01 was provided by KaiBioTech Co., Ltd. (Jeonju, Korea).

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