Feasibility and Therapeutic Potential of ^{177}Lu–Fibroblast Activation Protein Inhibitor–46 for Patients With Relapsed or Refractory Cancers

A Preliminary Study

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Introduction: Fibroblast activation protein (FAP) is a member of the serine protease family and has a high expression in the stroma of approximately 90% of epithelial malignancies. The present investigation aimed to assess the feasibility, safety, and dosimetry data of ^{177}Lu-FAPI-46 in diverse malignancies.

Patients and Methods: Patients with advanced cancers with nonoperable tumors, or tumors refractory to conventional therapies, were enrolled. Treatment included escalating doses of ^{177}Lu-FAPI-46 (1.85–4.44 GBq) per cycle using a combination of clinical and statistical expertise design, and intervals of 4 to 6 weeks were considered between the cycles. Biodistribution and dosimetry were examined by whole-body scans. We applied the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 to measure peptide-targeted radionuclide therapy (PTRT)–associated toxicity.

Results: A total of 21 patients (11 females and 10 males) with a median age of 50 years (range, 6–79 years) were investigated. Of 21 participants, 18 cases were selected for PTRT. Overall, 36 PTRT cycles were performed. The median number of PTRT cycles and the median injected amount of activity in each cycle were 2 and 3.7 GBq, respectively. The dosimetric analysis revealed median absorbed doses of 0.026, 0.136, 0.886, and 0.02 with ranges of 0.023–0.034, 0.001–0.2, 0.076–1.39, and 0.002–0.2 mGy/MBq for the whole body, liver, kidneys, and spleen, respectively. The therapy was well tolerated in almost all patients.

Conclusions: The findings of this preliminary investigation might indicate the potential feasibility and safety of PTRT using ^{177}Lu-FAPI-46 for different aggressive tumors. Moreover, the current study could be beneficial in determining the suitable amount of activity for a phase 2 study.

Key Words: peptide-targeted radionuclide therapy, ^{177}Lu-FAPI-46, theranostics, fibroblast activation protein

(*Clin Nucl Med* 2021;46: e523–e530)

Received for publication May 12, 2021; revision accepted May 16, 2021.

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Conflicts of interest and sources of funding: none declared.

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ISSN: 0363-9762/21/4611–e523
DOI: 10.1097/RLU.0000000000003810

Fibroblast activation protein (FAP) belongs to the serine protease family and is highly expressed in the stroma of almost 90% of epithelial malignancies. Consequently, inhibitors specific to FAP have been suggested as anticancer medications, and FAP has been regarded as potential imaging and therapeutic target in terms of theranostics in recent years.[1,2]

Recently, various investigations have evaluated the efficacy and biodistribution of FAP inhibitor (FAPI)–labeled ^{68}Ga PET/CT and showed significant uptake of FAPI in some malignancies.[3,4]

Fibroblast activation protein–targeted therapies using ^{177}Lu-DOTA.SA.FAPi, ^{225}Ac-FAPI-04, ^{153}Sm-FAPI-46, and ^{90}Y-FAPI-04 have been reported to be applied for treating malignancies.[5–8] The primary aim of the current study was to assess the feasibility, safety, and dosimetry data of peptide-targeted radionuclide therapy (PTRT) with ^{177}Lu-FAPI-46 in different malignancies. The second aim was to evaluate treatment outcomes regarding progression-free survival (PFS) and overall survival (OS).

PATIENTS AND METHODS

Patient Characteristics

A total of 21 patients whose cancer was confirmed by histopathology and who had a nonoperable metastatic tumor refractory to conventional therapies were enrolled in this study between December 2020 and May 2021. All the medical records of the patients, such as previous imaging, results of pathological and hematological tests, and previous treatments, were collected. All of the patients had a history of several courses of chemotherapy and/or external radiotherapy.

Inclusion and Exclusion Criteria

The inclusion criteria entailed confirmed progressive disease after standard approved treatments and positive FAPI expression of most lesions determined by FAPI-based imaging. The exclusion criteria encompassed clinically significant dysfunction of the liver, kidneys, or bone marrow, in addition to hemoglobin <9 g/dL, white blood cell count <2500/μL, platelet count <90 × 109/L, creatinine >2 mg/dL, bilirubin >1.5 UNL (upper normal limit), and alanine aminotransferase and aspartate aminotransferase > 2.5 UNL (>5 UNL lack of liver metastases). Moreover, patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥3; Karnofsky Performance Scale (KPS) score >40; congestive heart failure of class 3 or 4 New York Heart Association; active and uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy; and psychiatric illness/social situations that could interfere with study requirements were excluded.

The treatment decision for each patient was made by an interdisciplinary tumor board. The research protocol and experimental

nature of the treatment were explained to the patients and the patient's parents and/or legal representatives, and written consent was subsequently obtained from them. Treatments were based on compassionate care when no other therapeutic option was available. The study was carried out according to the Declaration of Helsinki and good clinical practice guidelines. Furthermore, it was approved by the Institutional Ethics Committee of the Bushehr University of Medical Science with the registration code of IR.BPUMS.REC.1399.130.

Baseline FAPI-46 Imaging

All participants underwent imaging with a ^{68}Ga-FAPI-46 PET/CT scan or ^{177}Lu-FAPI-46 scintigraphy pretreatment to confirm sufficient FAPI-46 expression.

^{68}Ga-FAPI-46 PET/CT Imaging Protocol

We used commercially available ^{68}Ge/^{68}Ga (PARSGalluGEN) generators (Pars Isotope Company, Iran) to obtain ^{68}Ga. The FAPI-46 kit was also afforded from this company. Radiolabeling and quality control for preparing ^{68}Ga-FAPI-46 were conducted based on the manufacturer standards.

Thirty minutes after injecting 148 to 185 MBq of ^{68}Ga-FAPI-46 through the IV route, acquisition was completed using PET/CT (Siemens Biograph mCT 128, Germany) with a total body field of view from vertex to midthigh. Nondiagnostic CT was carried out using a 4-mm slice thickness. The PET images were reconstructed using the iterative technique with ordered subset expectation maximization, 5-mm Gaussian filter size, as well as 2 iterations and 8 subsets.

The images were reviewed and interpreted by 2 nuclear medicine specialists who were blinded to the previous imaging results and nonblinded to the clinical history of the patients. Positive lesions were demonstrated according to visual and quantitative evaluation. Foci of uptake more than the adjacent background and not related to physiologic uptake were regarded as malignant lesions.

^{177}Lu-FAPI-46 Diagnostic Imaging

We completed ^{177}Lu-FAPI-46 imaging by means of a dual-head gamma camera (Vertex ADAC plus) equipped with a low-energy collimator with high resolution. Whole-body anterior and posterior images were obtained 60 minutes after the IV injection of 370 MBq (10 mCi) ^{177}Lu-FAPI-46. For ^{177}Lu-FAPI-46 SPECT, a symmetric 15% window was centered at 140 KeV. Images were recorded in a 256 × 256 matrix of words on a nuclear medicine computer. In the case of borderline abnormality, extra oblique-lateral views or SPECT images were taken of the early images followed by late planar imaging to improve the detectability of lesions. A nuclear medicine specialist investigated the projections for optimizing the quality of the images. Finally, the images were analyzed by 2 nuclear medicine specialists. Patients who had an augmented uptake in early or delayed images or both were considered as positive. The radionuclide uptake was characterized as no uptake (−), mild uptake (±), moderate uptake (+), and intense uptake (++).

All cases with at least 1 intense radiotracer uptake lesion on ^{177}Lu-FAPI-46 scintigraphy using a diagnostic dose (370 MBq) were candidates for PTRT with ^{177}Lu-FAPI-46. Furthermore, high FAPI expression on ^{68}Ga-FAPI-46 PET/CT was a criterion of consideration for PTRT.

^{177}Lu-FAPI-46 Therapy

Radiolabeled ^{177}Lu-FAPI-46 was procured from Pars Isotope Co, Iran. The patients selected for PTRT were hospitalized in the dedicated theranostics center of the department of nuclear medicine. According to the study protocol, a dose escalation scheme was evaluated, initiating at an activity of 1.4 GBq followed by 2.96, 3.7, and 4.44 GBq. Dose-limiting toxicity was defined as an attributable grade >3 hematotoxicity or grade >2 non-hematotoxicity.

All patients in each cycle of ^{177}Lu-FAPI-46 received 1.85 to 4.4 GBq. For PTRT, 10-mL normal saline was used to dilute the radiotracer. The ^{177}Lu-FAPI-46 was injected intravenously for 10 minutes under steroid and ondansetron coverage. The blood pressure and heart rate of the patients, along with the occurrence of any symptoms, were continuously documented. Intervals of 4 to 6 weeks were considered between the cycles.

In the event of any complications, disease progression, death, or unwillingness of the patient to continue participation, the treatment was ceased and considered as unsuccessful. We discussed the patient's condition after each cycle in a multidisciplinary team and decided for administration and the next interval. To avoid contamination, a urinary catheter was used for patients with urinary

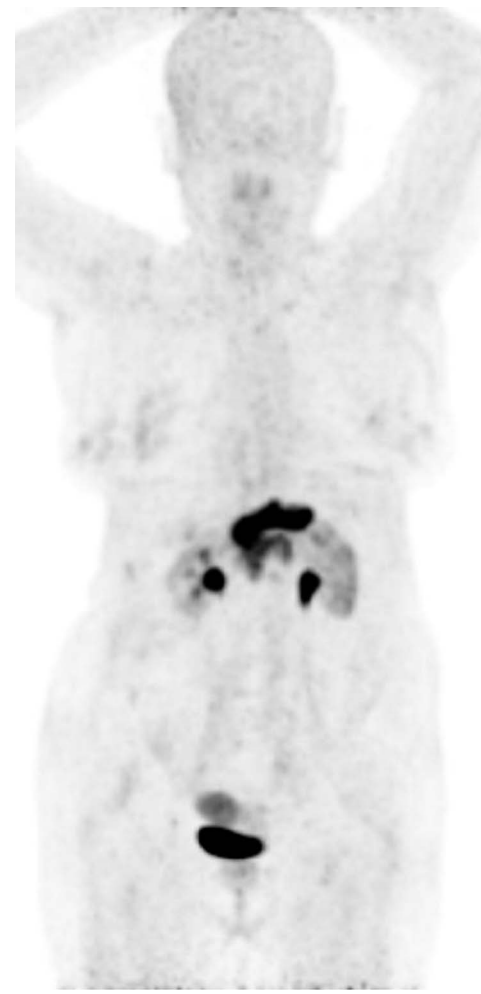

FIGURE 1. A 69-year-old woman with recurrent cholangiocarcinoma underwent ^{68}Ga-FAPI PET/CT. She could not perform ^{18}F-FDG because of uncontrollable diabetic hyperglycemia. The images revealed an intensely FAPI-avid (SUV_{max}, 24.5) soft tissue mass in the Whipple surgical bed along with several mildly FAPI-avid small peripancreatic lymph nodes and adjacent peritoneal nodules. A ^{68}Ga-FAPI–avid (SUVmax = 9.3) myoma was also detected in the uterus.

incontinence during the first 48 hours posttreatment. The patients were discharged when radiation emission was lower than 9 μSv/h at 2 m, which is commonly reached 2 to 4 hours after the first void.

Posttreatment Imaging

Scintigraphy was carried out up to 7 days postinjection to assess radiotracer biodistribution and dosimetry. It was completed using a dual-head gamma camera (Vertex ADAC plus) equipped with a low-energy, high-resolution collimator. The energy was set at 113 KeV with an energy window of 20%. Whole-body and SPECT acquisition scan modes were performed if required.

Biodistribution and Dosimetry

To evaluate biodistribution and dosimetry, a scan of the whole body was performed 2 (without voiding), 24, 48, 72, 96, 120, 144, and 168 hours after IV injection. Dosimetry analysis was conducted according to the procedures previously published.[9–11] Similar to the research by Kratochwil et al,[12] no attenuation correction was carried out. Dosimetry evaluation was performed for whole-body, liver, kidneys, and spleen. One expert nuclear medicine physicist drew all regions of interest on images after injection. The conjugate view technique was used to calculate radiotracer uptake for each of the desired organs,[13] and a time-activity curve was depicted for each organ. The dose absorbed to the organs was calculated by the OLINDA/EXM v1.0.[14]

Adverse Effects and Toxicity

Peptide-targeted radionuclide therapy–associated toxicity was assessed using laboratory tests, including hematology, renal function test (creatinine), and liver function test (aspartate aminotransferase and alanine aminotransferase) every 2 weeks after PTRT. This toxicity was measured according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). In terms of short-term adverse effects, the patients were monitored by weekly phone calls and were asked to inform us in case of any discomfort, including nausea, vomiting, fever, and/or headache.

Response Evaluation

The participants of the present study consisted of a small, heterogeneous group of patients who had very poor prognoses. Therapy was performed compassionately, and therefore, the patients were not evaluated by scheduled multimodality imaging. An individual approach was adopted for each patient based on imaging and/or laboratory tests. For measurable diseases, the Response Evaluation Criteria in Solid Tumors were applied. Moreover, ECOG status performance was evaluated monthly for estimating physical condition.

Data Collection and Statistical Analysis

We reported descriptive statistics, continuous variables, and categorical variables as median, range, and frequencies, respectively.

TABLE 1. Baseline Characteristics of All Patients

Patient	Sex/Age	Sur/Rad/Ch	Primary Tumor Site	Involvement	Diagnostic Modality
1	F/47	+/−/+	Ovary	Regional, peritoneum	Scintigraphy
2	M/38	+/+/+	Sarcoma	—	Scintigraphy and FDG PET
3	M/60	+/−/+	Colon	Liver, lymph node, bone, lung	Scintigraphy
4	F/47	+/+/+	Breast	Bone	Scintigraphy
5	F/44	+/+/+	Ovarian	Regional, peritoneum, bone	Scintigraphy
6	M/55	−/−/+	Lung	Regional, lymph node, bone, pleura	Scintigraphy
7	M/6	+/+/+	Sarcoma	Regional, bone	Scintigraphy
8	F/51	+/+/+	Breast	Liver, lymph node, bone, peritoneum, lung, pleura	Scintigraphy
9	M/79	−/−/+	Pancreas	Regional, liver, peritoneum, lymph node, bone, lung, pleura	FAPI PET
10	M/65	−/−/−	Prostate	Bone	Scintigraphy
11	F/35	+/+/+	Breast	Liver	Scintigraphy
12	F/52	+/+/+	Breast	lymph node, bone, lung	Scintigraphy
13	F/45	+/−/+	Cervical	Liver, lymph node, bone, lung	Scintigraphy
14	F/40	+/+/+	Breast	Liver, bone, lung	Scintigraphy
15	M/49	+/+/+	Prostate	—	Scintigraphy
16	M/28	+/−/+	Round-cell tumor	Liver, peritoneum, lymph node, bone	FAPI and FDG PET
17	F/50	+/−/+	Pancreas	Liver, lymph node, bone, lung	FAPI and FDG PET
18	M/71	−/+/−	Colon	Regional, liver, peritoneum, lymph node, bone, lung, pleura	Scintigraphy
19	M/70	+/+/+	ATC	Regional, lymph node, bone	FAPI PET
20	F/61	−/−/+	Colon	Regional, liver, peritoneum, lymph node, bone	Scintigraphy and FDG PET
21	F/69	+/+/+	Bile duct	Regional, peritoneum, lymph nodes	FAPI PET

F, female; M, male; Sur, surgery; Rad, external radiotherapy; Ch, chemotherapy; ATC, anaplastic thyroid cancer.

Progression-free survival was defined as the time from the initiation of treatment with ^{177}Lu-FAPI-46 until the first evidence of progression or relapse, or to death. Overall survival was defined as the time from the first tumor diagnosis until death due to any cause (OS-d). The OS from recurrence or conversion was defined as the duration since recurrence diagnosis in primary tumors or conversion in secondary, to death due to any cause (OS-r/c). The OS from the start of treatment was defined as the time since the first ^{177}Lu-FAPI-46 treatment cycle to death from any cause (OS-t). The Kaplan-Meier estimator was applied to calculate survival parameters.

We asked the individuals to categorize the alterations in their symptoms after ^{177}Lu-FAPI-46 treatment according to a 4-grade scale. In this scoring scale, excellent response, good response, moderate response, and poor response represented no symptoms, significant reduction in symptoms, slight decrease in symptoms, and no alteration or worsening of symptoms, respectively. Data were statistically analyzed using SPSS software version 21 (IBM Corporation, Somers, NY). *P* value less than 0.05 was considered statistically significant.

RESULTS

Twenty-one patients with advanced cancers, consisting of 10 males and 11 females, with a median age of 50 years (range, 6–79 years) were evaluated. The cancer types included ovarian cancer (n = 2), sarcoma (n = 2), colon cancer (n = 3), breast cancer (n = 5), pancreatic cancer (n = 2), prostate cancer (n = 2), cervical cancer (n = 1), round-cell tumor (n = 1), lung cancer (n = 1), anaplastic thyroid cancer (n = 1), and cholangiocarcinoma (n = 1). For FAP expression assessment, 5 of 21 cases underwent ^{68}Ga-FAPI-46 PET/CT, and 16 patients underwent scintigraphy with ^{177}Lu-FAPI-46 before administrating the therapeutic dose. Of 21 patients, 19 cases demonstrated intense FAP uptake on PET or SPECT and were selected for PTRT. One of the patients who had recurrent cholangiocarcinoma and an intensely FAPI-avid (SUV_{max}, 24.5) soft tissue mass in the midabdomen contracted severe COVID-19 and died before receiving ^{177}Lu-FAPI-46 (Fig. 1). The remaining 18 participants with positive scans presented with metastases to the surrounding region (n = 8), liver (n = 10), peritoneum (n = 8), lymph node (n = 11), bone (n = 16), lung (n = 9), and pleura (n = 4).

Treatment included escalating doses of ^{177}Lu-FAPI-46 (1.85–4.44 GBq) per cycle using a combination of clinical and statistical expertise design. The first 4 patients received 1.85 GBq per cycle. The 5 next individuals received a higher dose of 2.96 GBq per cycle. For the next 20 cycles, 3.7 GBq per cycle was applied, and in the last 3 cycles, the patients received 4.44 GBq per cycle. A child with rhabdomyosarcoma received a fixed dose of 1.85 GBq in 4 cycles.

In total, 36 PTRT cycles were performed in 18 cases. The medians of PTRT cycles and total injected activity were 2 and 6.1 GBq with ranges of 1 to 4 and 1.85 to 13.7 GBq, respectively. The median amount of activity in each cycle was 3.7 GBq (range, 1.85–4.44). The baseline characteristics of the patients are

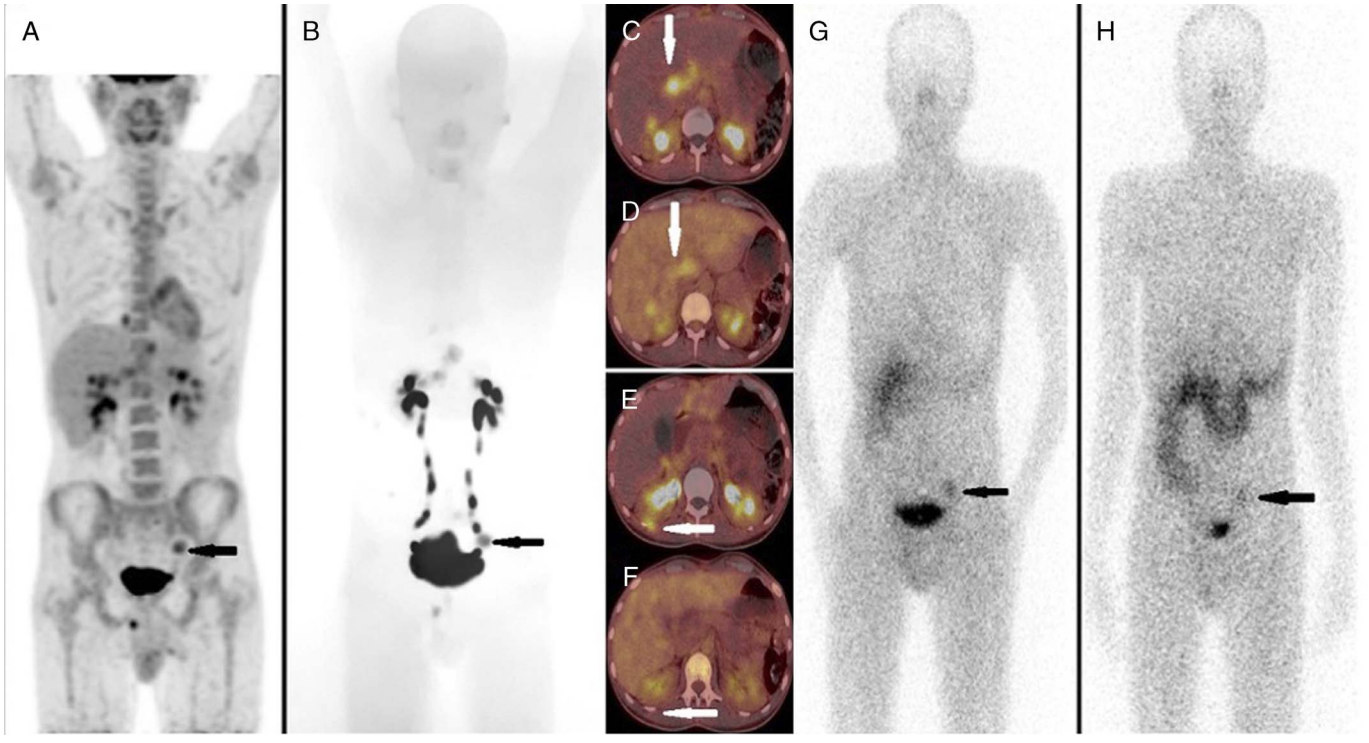

FIGURE 2. A 28-year-old man with desmoplastic small round cell tumor with prior history of abdominal surgery and chemotherapy underwent ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT. ^{18}F-FDG revealed FDG-avid metastases in the right paracardiac lymph node, several abdominal, and pelvic lesions, liver, and right hemiscrotum (**A**). ^{68}Ga-FAPI PET/CT revealed almost the same FAP-avid lesions observed in ^{18}F-FDG (**B**). The SUV_{max} of the lesions on ^{68}Ga-FAPI PET/CT (white arrows) (**C**) were higher in intensity rather than on FDG PET/CT (white arrows) (**D**), and also 1 lesion in the posterior abdomen, which was visualized on ^{68}Ga-FAPI PET/CT (white arrows) (**E**), did not show any uptake on FDG PET/CT (white arrows) (**F**). In contrary, the lesion in the mediastinum had higher resolution on FDG PET/CT rather than ^{68}GA-FAPI PET/CT. The patient underwent 2 cycles of PTRT (6.6 GBq). Posttherapy scintigraphy after the first cycle (**G**) showed radiotracer uptake in lesions. According to the posttherapy scintigraphy of the second cycle (**H**), a decrease in uptake of the left pelvic lymph node involvement (dark arrows) was observed, but the patient was considered stable in total.

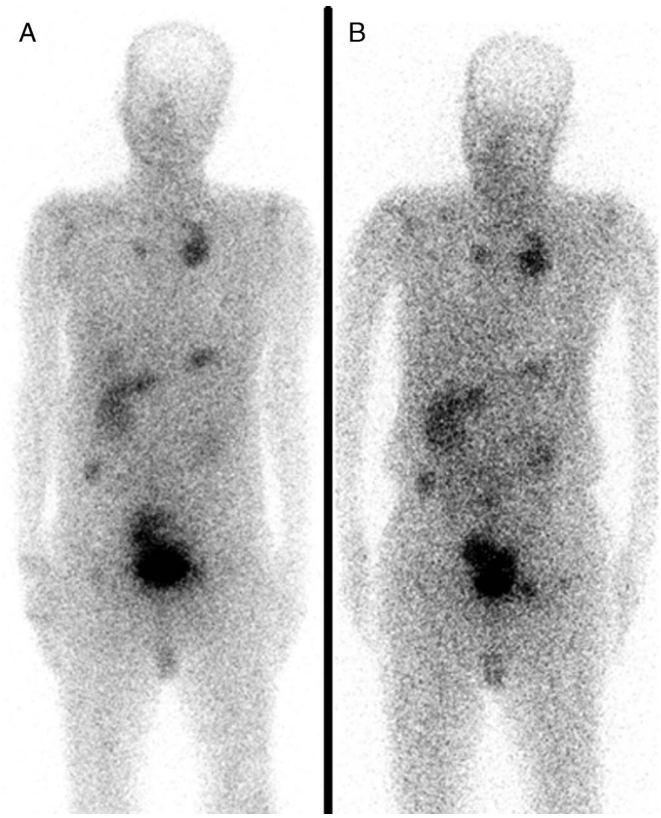

FIGURE 3. A 60-year-old man with metastatic colon cancer with a prior history of surgery and chemotherapy underwent scintigraphy with a diagnostic dose of ^{177}Lu-FAPI-46 that revealed multiple FAPI-avid lesions in the liver, lymph node, bone, and lung (**A**). The patient underwent 2 cycles of PTRT with ^{177}Lu-FAPI-46 (3.7 GBq per cycle) resulting in stable disease. The patient was still alive after follow-up 5.5 (**B**).

presented in Table 1. Figures 2 and 3 indicate the PTRT process in 2 studied cases.

Toxicity

The therapy was well tolerated in all patients. According to the CTCAE, grade 3 anemia, grade 1 thrombocytopenia, and grade 1 leukopenia were observed in 1 patient with sarcoma. This patient had received concomitant chemotherapy during PTRT. All of the other patients showed no hematotoxicity, nephrotoxicity, or hepatotoxicity. One patient with breast cancer complained of increased bone pain after the therapy. None of the patients had nausea or vomiting. We observed no changes in their blood pressure or heart rate values over the inpatient admission. Table 2 shows the treatment profiles and responses of all the patients.

Dosimetry

In this study, dosimetry was performed for 11 patients. According to the posttherapy images, minimal uptake of the radiotracer was observed in normal tissues and organs. The median absorbed dose to the whole body was 0.026 (range, 0.023–0.034), liver was 0.136 (range, 0.001–0.2), kidneys was 0.886 (0.076–1.39), and spleen was 0.02 (0.002–0.2) mGy/MBq (Table 3). Figure 4 indicates the results of the dosimetry.

Response

At the time of analysis, 12 of the patients showed stable disease with no significant change in clinical condition, but 6 showed progressive disease. The median OS time from the primary diagnosis (OS-d) was 25.0 months (range, 6.0–110.0) and from the diagnosis of the recurrence/refractory (OS-r) was 9.0 months (range, 5.0–30.0). From the start of treatment with ^{177}Lu-FAPI-46, 16 patients are still alive, and 2 patients with pancreas and cervical cancers have died due to disease progression. The median PFS was 3.0 months (range, 1.0–6.0), and the OS-t was 4.0 months (range, 1.0–6.0) at the time of analysis.

According to the 4-grade subjective scale responses, 6/18 (33.33%) and 12/18 (66.66%) of the patients showed moderate and poor responses, respectively. According to the short follow-up assessment of the 18 patients, 12 showed stable disease and 6 showed progressive disease.

The median ECOG and KPS index before PTRT were 1 (0–2) and 75 (50–100), respectively; no change was observed after PTRT ($P > 0.05$).

DISCUSSION

The most important finding of this study underscores the potential feasibility and safety of PTRT with ^{177}Lu-FAPI-46 in patients with metastatic cancers.

According to the dosimetric and biodistribution analysis, minimal uptake in normal tissues and organs, and acceptable uptake with long retention in tumoral regions was observed, indicating that the safety of PTRT with ^{177}Lu-FAPI-46 is similar to common theranostics agents such as ^{177}Lu-DOTATATE for neuroendocrine tumors[15] and ^{177}Lu-PSMA for prostate cancer.[16] In this study, the median absorbed doses (whole body, 0.026 [range, 0.023–0.034]; liver, 0.136 [range, 0.001–0.2]; kidneys, 0.886 [0.076–1.39]; and spleen, 0.02 [0.002–0.2] mGy/MBq) roughly correlate to those noted in previous studies.[17,18] In 1 study, the resulting absorbed doses of PTRT with ^{177}Lu-FAP-2286 in the whole body, red marrow, and kidneys were 0.05–0.1, 0.04–0.09, and 0.6–0.9 Gy/GBq, respectively; high specific tumor uptake with long retention was observed in all patients according to delayed imaging (up to 10 days).[17] Given the dosimetry analysis by Kuyumcu et al,[18] the mean absorbed doses per MBq after administration of a low dose of ^{177}Lu-FAPI-04 were 0.25 ± 0.16 mGy (range, 0.11–0.47 mGy), 0.11 ± 0.08 mGy (0.06–0.22 mGy), and 0.04 ± 0.002 mGy (0.04–0.046 mGy) for kidneys, liver, and bone marrow, respectively.

According to the CTCAE, in this study, grade 3 anemia, grade 1 thrombocytopenia, and grade 1 leukopenia were observed in 1 patient with sarcoma in whom concomitant chemotherapy with PTRT was continued. The evidence generated by this trial indicated that PTRT was well tolerated in most patients, and similar to ^{177}Lu-DOTATATE and ^{177}Lu-PSMA, PTRT is a safe therapy method with minimal adverse effects.[19–22]

Endoradiotherapy using chelating ligands with high affinity to FAPI have been developed for imaging (^{68}Ga-FAPI-46 and ^{177}Lu-FAPI-46) to translate this concept into metastatic patients. In recent years, several studies have been performed on the diagnostic efficacy of ^{68}Ga-FAPI on several types of cancers,[3,4,23] which showed a high tumor-to-background ratio and rapid renal clearance, indicating the high potential of FAPI in cancer management. FAPI-PET, as compared with ^{18}F-FDG, has no fasting or specific dietary preparation, leading to compliance of patients, such as diabetic patients, who are unable to perform an FDG PET/CT due to hyperglycemia. This was the case for 1 of our patients who died as a result of a severe COVID-19 infection before receiving the final dose of ^{177}Lu-FAPI-46 (Fig. 1).

Another important advantage of FAPI is its theranostic role.[24–26] There are very few published studies and case reports

TABLE 2. ^{177}Lu-FAPI-46 Treatment Profile and the Treatment Response in All Patients

Patient	PTRT Cycle	CA (GBq)	ECOG (Pretreatment and Posttreatment)	KPS (Pretreatment and Posttreatment)	Response	Toxicity	Survival at the Time of Analysis, mo	Alive
1	1	3.7	0/0	90/90	SD	—	5.50	Yes
2	—		—	—	—	—	—	—
3	2	7.4	2/2	60/60	SD	—	5.50	Yes
4	1	2.96	2/2	60/60	SD	—	4.50	Yes
5	3	10	0/0	90/90	SD	—	4.50	Yes
6	4	13.7	1/1	80/80	SD	—	4.50	Yes
7*	4	8.5	1/1	70/70	PD	Thrombocytopenia (G1), leukopenia (G1), anemia (G3)	4.50	Yes
8	4	12.95	1/2	80/60	PD	—	4.50	Yes
9	2	5.55	2/2	60/50	PD	—	4.00	No
10	1	1.85	0/0	90/90	SD	—	4.50	Yes
11	1	1.85	0/0	100/100	SD	—	4.50	Yes
12	3	11.1	2/1	70/80	SD	—	4.50	Yes
13	2	6.66	1/1	80/80	PD	—	2.00	No
14	2	7.4	1/1	80/80	PD	—	2.00	Yes
15	—		—	—	—	—	—	Yes
16	2	6.66	0/0	90/90	SD	—	1.30	Yes
17	1	3.7	2/2	60/90	PD	—	2.00	Yes
18	1	3.7	2/2	50/90	SD	—	1.00	Yes
19	1	3.7	1/1	70/90	SD	—	1.00	Yes
20	1	3.7	2/2	50/90	SD	—	1.00	Yes
21†	—	—	—	—	—		—	—

*The patient had received concomitant chemotherapy and ^{177}Lu-FAPI-46 therapy.

†The patient died before taking ^{177}Lu-FAPI-46 due to severe COVID-19 disease.

CA, cumulative amount of activity; SD, stable disease, PD; progressive disease; G1, grade 1; G3, grade 3.

TABLE 3. Results of Dosimetric Analysis of ^{177}Lu-FAPI-46 (mGy/MBq)

	Whole Body	Liver	Kidneys	Spleen
1	0.027	0.015	0.131	0.003
2	0.030	0.012	0.12	0.003
3	0.025	0.001	0.083	0.002
4	0.026	0.136	0.98	0.02
5	0.026	0.011	0.076	0.002
6	0.031	0.178	1.24	0.03
7	0.029	0.192	1.07	0.2
8	0.023	0.144	1.11	0.02
9	0.034	0.185	1.39	0.03
10	0.026	0.205	0.773	0.02
11	0.024	0.13	0.886	0.03
Median (range)	0.026 (0.023–0.034)	0.136 (0.001–0.2)	0.886 (0.076–1.39)	0.02 (0.002–0.2)

showing the therapeutic efficacy of radiolabeled FAPI. In a retrospective study, the feasibility, biodistribution, and dosimetry of PTRT with ^{177}Lu-FAP-2286 in different malignancies were evaluated in 11 patients after prior confirmation of significant tumor uptake with ^{68}Ga-FAPI PET; the therapies were well tolerated, and no significant short-term adverse effects occurred. A decrease in pain was reported in 3 patients.[17] Ballal et al[5] reported the efficacy of 1 cycle of PTRT with ^{177}Lu-DOTA.SA.FAPI (3.2 GBq) in a 31-year-old woman with metastatic breast cancer, leading to a decrease in the intensity of headache, which was due to brain metastasis.

Among the patients in the current study, 6/18 (33.33%) showed moderate responses with a slight decrease of symptoms. According to the short follow-up assessment, 2 pattern of responses were observed 6 cases with progressive disease and 12 cases with stable disease. In total, the ECOG and KPS demonstrated no significant change after treatment. As expected in a phase 1 trial, this study is aiming for very initial signs of efficacy, but it should be kept in mind that the patients were in a late stage of the disease, which leads to rather low expectations regarding the efficacy observed.

It should be mentioned that the survival parameters (such as PFS and OS) of patients with prostate cancer and neuroendocrine tumors are usually longer than other cancers, such as those studied in the current project. In other words, it might mean that we need to make great strides to individualize radiotheranostic approaches in terms of types of cancers, intervals between cycles, injected radionuclide doses, types of radionuclides, and types of FAPIs, mostly upon time of tumoral retention, which should be a focus of future studies that propose ^{177}Lu-FAPI therapy.

Although, as mentioned previously, FAPI has high potential for diagnosing a wide variety of cancers, diverse factors limit the application of FAPI as a therapeutic agent, such as concern about the low FAPI retention time, which was found in FAPI-02 and FAPI-04. However, it should be noted that other FAPI compounds, such as FAPI-46, present high tumor uptake and longer retention with lower uptake in normal organs in comparison with FAPI-04, which make it promising for cancer treatment.[1,2,25] Another technique to compensate for the low retention time of FAPI is to use radiopharmaceuticals with a shorter half-life and high-energy β-emitters, such as ^{188}Re. We have taken them into consideration for future patients.[25,27]

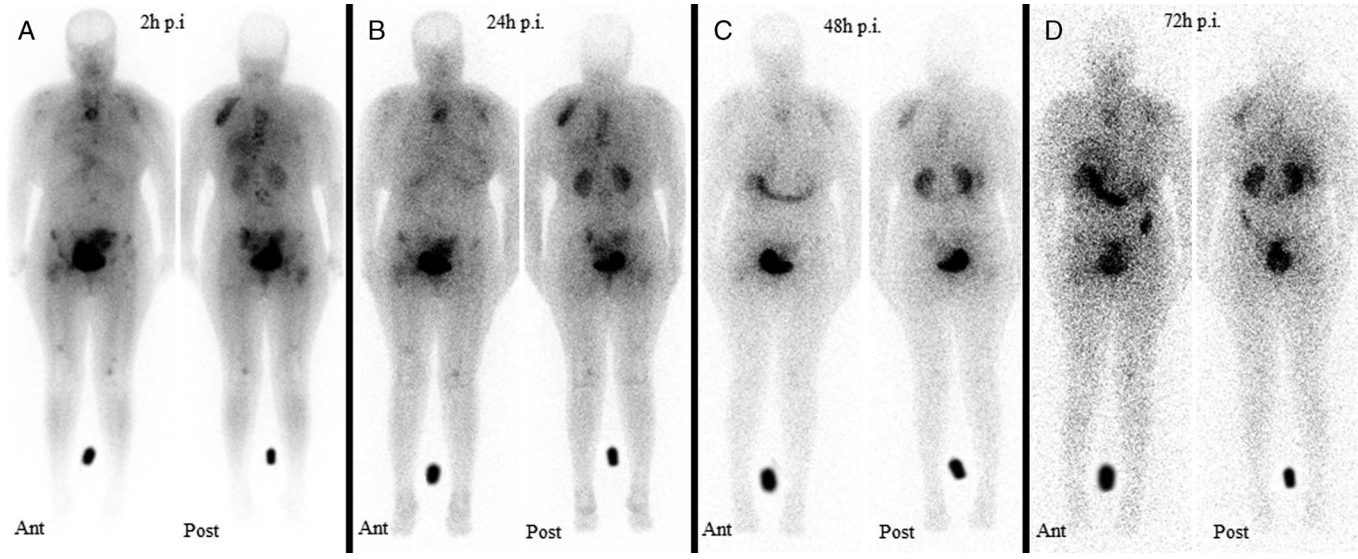

FIGURE 4. Planar scintigraphy (anterior and posterior views) after therapeutic application of ^{177}Lu-FAPI-46 at 2 hours (before voiding) (**A**), 24 hours (**B**), 48 hours (**C**), and 72 hours (**D**) postinjection in a 52-year-old patient with breast cancer. The images revealed several FAP-avid lesions throughout the body and tumor retention of ^{177}Lu-FAPI-46 in the lesions.

This research had some limitations, the most important of which were the small sample size and short follow-up. However, the main aim was to assess the potential feasibility and safety of ^{177}Lu-FAPI-46 therapy. The included participants had high heterogeneity with diverse cancers and variable treatment regimes.

After this preliminary investigation, the authors plan to assess ^{177}Lu/^{188}Re-FAPI in a more homogeneous group of patients with more favorable performance status. Individualized dosimetry and profile genomics will be among the fundamental features of future trials.

CONCLUSIONS

According to the findings of this preliminary study, ^{177}Lu-FAPI-46 has potential logistic and radiation safety advantages in patients with metastatic, highly aggressive tumors. In addition to demonstrating the tolerability of ^{177}Lu-DOTA-FAPI-46, our results may be beneficial in planning further well-designed trials on more homogeneous groups of participants with advanced cancer.

ACKNOWLEDGMENTS

The authors of the present study would like to express their gratitude to the participants, parents, legal representatives, and health care personnel from diverse therapeutic centers for their generous support and cooperation in the evaluation of this novel treatment. This investigation was granted by Bushehr University of Medical Sciences, Iran.

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