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Initial Findings on the Use of [^{225}Ac]Ac-DOTATATE Therapy as a Theranostic Application in Patients with Neuroendocrine Tumors

Nöroendokrin Tümörlü Hastalarda Bir Teranostik Uygulama Olarak [^{225}Ac]Ac-DOTATATE Tedavisi: İlk Bulgular

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Abstract

Objectives: This study aimed to evaluate the stability, safety, and efficacy of alpha-targeted therapy with [^{225}Ac]Ac-DOTATATE in patients with grade 1/2 metastatic neuroendocrine tumors (NETs).

Methods: This retrospective cohort included patients (n=11) with metastatic NETs from different primary sites (bronchial, pancreatic, non-pancreatic gastroenteropancreatic NETs, paraganglioma, and unknown primary site) treated with [^{225}Ac]Ac-DOTATATE with a mean activity of 8.2±0.6 MBq (range: 7.5-10.0 MBq) at our institution between November 2019 and March 2022. The *in vivo* and *in vitro* stability of [^{225}Ac]Ac-DOTATATE was calculated. The safety profile was evaluated according to the CTCAE-v5.0. Treatment efficacy was evaluated according to [^{68}Ga]Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) images and the RECIST 1.1 criteria.

Results: Patients had 73% (n=8) lymph node metastases, 91% (n=10) liver metastases, 36% (n=4) lung metastases, and 73% (n=8) bone metastases. All but one patient was refractory to treatment with [^{177}Lu]Lu-DOTATATE. [^{225}Ac]Ac-DOTATATE was stable for at least 5 h *in vitro* (in saline) and 3 h *in vivo* (urine and blood samples). Grade 2 renal toxicity and grade 2 hematotoxicity were observed in one patient. No grade 3-4 toxicities were reported. According to post-treatment [^{68}Ga]Ga-DOTATATE PET/CT (n=9), 11% (n=1) had progressive disease, 44.4% (n=4) had stable disease, and 44.4% (n=4) had a partial response. The disease control rate was 89% (n=8). The median progression-free survival estimated according to Kaplan-Meier analysis was 12 months.

Conclusion: The preliminary results of this study suggest that [^{225}Ac]Ac-DOTATATE is stable, safe, and effective for treating advanced and [^{177}Lu]Lu-DOTATATE-refractory NETs. However, prospective studies are needed to determine the impact of treatment on overall survival and to uncover potential side effects.

Keywords: [^{225}Ac]Ac-DOTATATE, ^{225}Ac targeted alpha therapy, neuroendocrine tumors, peptide receptor radionuclide therapy, theranostic

Öz

Amaç: Bu çalışmanın amacı, grade 1/2 metastatik nöroendokrin tümörler (NET'ler) tanılı hastalarda [^{225}Ac]Ac-DOTATATE ile alfa hedefli tedavinin stabilitesini, güvenliğini ve etkinliğini değerlendirmektir.

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Yöntem: Primer tanıları bulunan (bronşiyal, pankreatik, non-pankreatik gastroenteropankreatik NET'ler, paraganglioma ve primeri bilinmeyen) metastatik NET olan ve Kasım 2019 ile Mart 2022 arasında kliniğimizde tedavi edilen hastalar retrospektif olarak incelendi. Hastalara ortalama 8,2±0,6 MBq (aralık: 7,5-10,0 MBq) aktivite ile [225Ac]Ac-DOTATATE tedavisi uygulandı (n=11). [225Ac]Ac-DOTATATE'in *in vivo* ve *in vitro* stabilitesi hesaplandı. Güvenlik profili CTCAE-v5.0'a göre değerlendirildi. Tedavi etkinliği [68Ga]Ga-DOTATATE pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) görüntüleri ve RECIST 1.1 kriterlerine göre değerlendirildi.

Bulgular: Hastaların %73'ünde (n=8) lenf nodu metastazı, %91'inde (n=10) karaciğer metastazı, %36'sında (n=4) akciğer metastazı ve %73'ünde (n=8) kemik metastazı bulunuyordu. Hastaların bir tanesi hariç tümü, [177Lu]Lu-DOTATATE ile tedaviye dirençliydi. [225Ac]Ac-DOTATATE, in vitro (salin içinde) en az 5 saat ve in vivo (idrar ve kan örnekleri) en az 3 saat boyunca stabil kaldı. Bir hastada grade 2 böbrek toksisitesi ve grade 2 hematotoksisite gözlendi. Grade 3-4 toksisite izlenmedi. Tedavi sonrası [68Ga]Ga-DOTATATE PET/BT'ye (n=9) göre, %11'inde (n=1) progresyon, %44,4'ünde (n=4) stabil hastalık ve %44,4'ünde (n=4) kısmi yanıt gözlendi. Hastalık kontrol oranı %89 (n=8) idi. Kaplan-Meier'e göre tahmini medyan progresyonsuz sağkalım 12 aydı.

Sonuç: Bu çalışmanın ön sonuçları, [225Ac]Ac-DOTATATE'in ileri evre ve [177Lu]Lu-DOTATATE tedavisine dirençli NET'lerin tedavisinde stabil, güvenli ve etkili olduğunu ortaya koymaktadır. Bununla birlikte, tedavinin genel sağkalım üzerindeki etkisini belirlemek ve olası yan etkileri ortaya çıkarmak için prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: [225Ac]Ac-DOTATATE, 225Ac hedeflenmiş alfa tedavi, nöroendokrin tümörler, peptid reseptör radyonüklit tedavi, teranostik

Introduction

For neuroendocrine tumors (NETs), early-stage surgery remains the only treatment option for complete cure (1,2). Because of the clinically silent course of the disease at onset, approximately 50% of patients are not detected until the advanced stage (1,3). However, in the metastatic stage, there are few effective treatment options, including long-acting somatostatin analogs, sunitinib, a multicentric tyrosine kinase inhibitor, and everolimus, an mTOR inhibitor (4,5,6,7).

Peptide receptor radionuclide therapy (PRRT) is a molecularly targeted treatment approach in which radiolabeled peptides with high affinity for somatostatin receptors are administered systemically. In the last 20 years, it has been successfully used for metastatic and unresectable NETs (8). Among the numerous alternatives, Lutetium-177 [177Lu] has emerged as the preferred radionuclide due to its favorable toxicity profile. After 20 years of experience, there is a growing body of evidence supporting the efficacy of PRRT (9,10). NETTER-1, a phase 3 study with [177Lu]Lu-DOTATATE, is the most important study to date. Patients treated with [177Lu]Lu-DOTATATE had an estimated median progression-free survival (PFS) of 40 months in the NETTER-1 trial, whereas patients treated with 60 mg octreotide-LAR had a PFS of only 8.4 months (11). However, despite high somatostatin receptor expression, a substantial number of patients develop resistance to targeted beta therapy after intensive treatment with [177Lu]Lu-DOTATATE (9,10,11,12).

In PRRT, targeted alpha therapy (TAT) has proven to be a viable alternative to targeted beta therapy. The use of alpha emitters for cancer therapy has two advantages over the use of beta emitters in PRRT. Because alpha particles have a short range of only a few cell diameters (0.1 mm), they can selectively ablate cancer cells while sparing healthy tissue (13,14). In addition, the higher linear energy transfer (LET) compared with typical beta emitters causes complicated DNA double-strand and DNA cluster breaks that eventually lead to cell death. Despite these advantages, there are limited data on the efficacy of TAT for treating NETs (15). In this study, we aimed to evaluate the safety and efficacy of treatment with [225Ac]Ac-DOTATATE in patients who did not respond to all other available treatments, including [177Lu]Lu-DOTATATE.

Materials and Methods

Patients

From November 2019 to March 2022, patients (n=11) treated with [225Ac]Ac-DOTATATE were enrolled in this retrospective study. All patients had a histopathological diagnosis of NETs and tumor progression prior to alpha therapy. Institutional inclusion criteria for PRRT were white blood cell (WBC) count >2000, platelet (PLT) >75000, red blood cell >3,000,000, hemoglobin (Hb) >6 mmol/L, serum creatinine level <2 mg/dL, and Karnofsky performance status >50. All patients had high uptake in all metastatic lesions on [68Ga]Ga-DOTATATE positron emission tomography/computed tomography (PET/CT), which was higher than uptake in the liver. Radiological evidence of disease progression according to [68Ga]Ga-DOTATATE PET/CT and the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 to determine tumor progression at baseline.

This study was approved by the Yeditepe University Clinical Research Ethics Committee (decision no: 1633, date: 06.07.2022).

Preparation of [225Ac]Ac-DOTATATE

[225Ac]$AcCl_3$ and [225Ac]$Ac(NO_3)_3$ were provided by ORNL, Oak Ridge USA IPPE JSC, Obninsk, Russia. In-house radiolabeling was performed in a hot cell using [225Ac]

(1 MBq/14 nmol ligand) with 0.1 M Tris buffer and 20% ascorbic acid. Radiolabeling was performed at 95 °C for 25 minutes (min). After cooling the reaction vessel to room temperature, 0.5-1.0 mL of sterile DTPA solution (3 mg mL-1 DTPA in saline) was added to the reaction vessel. This preparation was sterile filtered (0.22 µM) under aseptic conditions and then made up to 5-6 mL with sterile saline. The integrity of the filter was checked using a bubble point test. The radiochemical yield was determined by instant thin-layer chromatography (ITLC) on silica gel with 0.05 M citric acid as the solvent. The radiochemical yield was determined by measuring the activity of 218-keV-γ emission of [221Fr] on the upper and lower parts of the strip using a Captus 3000 well-type gamma counter (Capintec Inc, NJ, USA) after 45 min of labeling. The measured radiochemical yields of [225Ac]Ac-DOTATATE were over 97% after 45 min of labeling.

Stability of [225Ac]Ac-DOTATATE

One MBq of [225Ac]Ac-DOTATATE was incubated in saline at 37 °C for up to 5 h (n=3). At specific time points, the incubation solution sample was injected into reversed-phase high-pressure liquid chromatography (RP-HPLC) to investigate the *in vitro* stability of [225Ac]Ac-DOTATATE. The HPLC fractions were measured in the gamma counter at least 20 h after collection. The measured counts of the fractions with 440 keV γ-emission of [213Bi] were plotted in agreement with their tube counts obtained from RP-HPLC analysis. In the first 3 patients, in vivo stability was checked using blood samples obtained 0-10 min after injection of [225Ac]Ac-DOTATATE and urine samples obtained up to 3 h after injection. Blood samples collected from patients were precipitated with acetonitrile (1:1) and shaken. The precipitate was separated by centrifugation (5 min at 14,680 rpm). For analysis by RP-HPLC, the supernatant was diluted with double-distilled water (1:1) and then injected into RP-HPLC. The collected urine samples from patients were diluted with bi-distilled water, filtered, and immediately analyzed using RP-HPLC. The amount of [225Ac]Ac-DOTATATE excreted was calculated using standard samples prepared at the time of injection. The excretion rate was calculated using the injected amount of [225Ac]Ac-DOTATATE activity. The measured counts from the fractions were plotted according to their tube number from the analysis of RP-HPLC.

Treatment

All therapies were performed on an inpatient basis. To protect the kidneys, patients were administered a total of 500-1,000 mL of a 2.5% arginine and 2.5% lysine amino acid solution for 4 h starting 30 min before the injection of [225Ac]Ac-DOTATATE. Thirty min before therapy, 8 mg of ondansetron was administered to prevent nausea. [225Ac]Ac-DOTATATE was administered over 5 min with slow injection. The amount of injected activity was 100-120 kBq/kg, as adapted from Kratochwil et al. (16). Whole-body images were obtained 4 h after administration of therapies with gamma energies of [221Fr] and [213Bi]. Patients were observed every 60 min for 5 h to record vital signs such as blood pressure, fever, and pulse rate. In addition, patients were monitored for any complaints of pain, vomiting, and nausea for 24 h according to the standard institutional protocol for all inpatient treatments.

Response Evaluation, Survival, and Toxicity

Response to [225Ac]Ac-DOTATATE treatment was assessed by [68Ga]Ga-DOTATATE PET/contrast enhanced (ce) CT performed within 4 weeks before and 12-16 weeks after treatment. Treatment efficacy was assessed according to images from [68Ga]Ga-DOTATATE PET/CT and RECIST 1.1 criteria (17) using ceCT images from PET/CT. [68Ga]Ga-DOTATATE PET/CT was repeated 12-18 weeks after each treatment cycle and until clinical progression or death. PFS was calculated from the date of first administration of [225Ac]Ac-DOTATATE. The disease control rate was calculated as the percentage of patients who had a complete, partial, or stable response to treatment. Adverse events were documented three months after each cycle of [225Ac]Ac-DOTATATE treatment according to the Common Terminology Criteria for Adverse Events version 5 (18).

Statistical Analysis

The PFS calculation was based on Kaplan-Meier curves, whereas numerical outcome comparisons were performed with the Wilcoxon rank sum test using SPSS version 21 (IBM Corp., Armonk, NY, USA). Comparative assessment of response evaluation statistics was calculated using the chi-square test. A p-value of less than 0.05 was considered significant. Numerical results are presented as mean ± standard deviation.

Results

Patient Population

Within the patient cohort (n=11), 3 (27%) patients had pancreatic cancer NET, 1 (9%) had pulmonary NET, 3 (27%) had non-pancreatic gastroenteropancreatic-NET, 3 (27%) had NET with unknown primary tumor, and 1 had paraganglioma (Table 1). Ki-67 indexes were available only in 7 patients, and World Health Organization (WHO) classification was evaluated in 9 patients. Patients were previously treated with a median of 7.5 cycles of [177Lu]Lu-DOTATATE and multiple lines of chemotherapy. One patient received 3 cycles, 5 patients received 2 cycles, 6 patients

received 1 cycle of [225Ac]Ac-DOTATATE treatment. A total of 17 cycles of [225Ac]Ac-DOTATATE were administered. Patients received a median of one cycle of [225Ac]Ac-DOTATATE (range: 1-3) with mean activity of 8.2±0.6 MBq (range: 7.5-10.0 MBq). The mean time between different doses of [225Ac]Ac-DOTATATE treatment was 125±76 days. Some patients could not take up the treatment on time because of 225Ac supply shortages and travel restrictions during the coronavirus disease-2019 pandemic. At baseline, all patients showed tumor progression according to [68Ga]Ga-DOTATATE PET/CT. According to the WHO classification of NETs, 2 (20%) patients had grade 1, 7 (70%) patients had grade 2 (Ki-67 index range: 10-18%), 1 (10%) patient had unknown grade, and 1 patient had paraganglioma. The locations of metastases and previous therapies are listed in Table 1.

Table 1. Patient characteristic

Patients		
Age		
Mean (years)		59.0±11.9
Range		43-79
Gender	Male/female	8/3
Previous therapies		
Long acting somatostatin analogues		10 (91%)
Chemotherapy		11 (100%)
Radioembolizetion/chemoembolization to liver		6 (55%)
MIBG treatment		2 (18%)
[177Lu]Lu-DOTATATE		10 (91%)
WHO grade		
Grade 1 NET		2 (20%)
Grade 2 NET		7 (70%)
Unknown		1 (10%)
Location of primary tumor		
Lung		1 (9%)
Pancreas		3 (27%)
Non-pancreatic GEP-NET		3 (27%)
Paraganglioma		1 (9%)
Unknown primary		3 (27%)
Sites of metastases		
Lymph nodes		8 (73%)
Liver		10 (91%)
Lung		4 (36%)
Bone		8 (73%)

MIBG: Meta-iodobenzylguanidine, NET: Neuroendocrine tumor, GEP-NET: Gastroenteropancreatic neuroendocrine tumor

Stability of [225Ac]Ac-DOTATATE

RP-HPLC analyzes of the saline incubation samples showed a single radioactivity peak corresponding to [225Ac]Ac-DOTATATE. However, a slight decrease in the in vitro stability of [225Ac]Ac-DOTATATE was observed in the RP-HPLC analysis after 5 h of incubation in saline. A chromatogram of one of the samples RP-HPLC is shown in Figure 1. A slight decrease in the in vitro stability of [225Ac]Ac-DOTATATE was also observed in ITLC analysis, but the radiochemical yield was still higher than 96% after 5 h of incubation in saline solution.

RP-HPLC analyzes of the blood and urine samples showed a single radioactivity peak corresponding to [225Ac]Ac-DOTATATE, but a slight decrease in stability *in vivo* was also observed in the blood and urine samples after injection (Figure 2). The mean excretion rate of [225Ac]Ac-DOTATATE

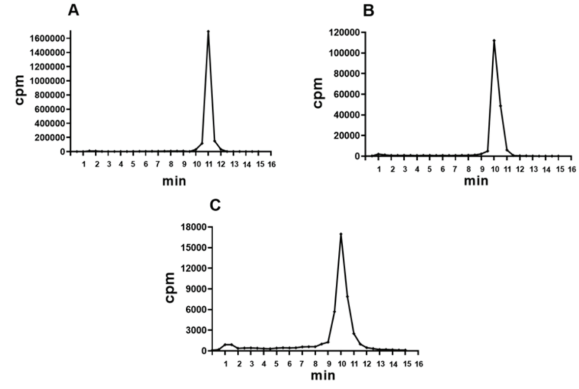

Figure 1. Reversed-phase high-pressure liquid chromatography profiles of 1 MBq [225Ac]Ac-DOTATATE from reaction vessel **A)** after incubation in saline, **B)** after 3 hours, **C)** after 5 hours

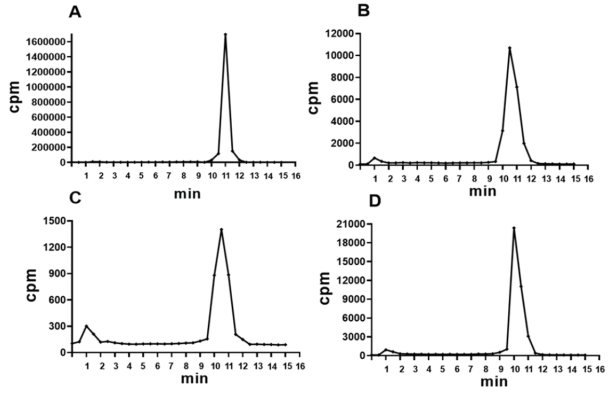

Figure 2. Reversed-phase high-pressure liquid chromatography profiles of [225Ac]Ac-DOTATATE A) from the reaction vial B) in blood after injection of 10 MBq of radioligand in a patient after 0-10 min C) in urine after injection of 10 MBq of radioligand in a patient after 1 h D) in urine after injection of 10 MBq of radioligand in a patient after 3 h

from the kidneys 24 h after injection was 56±9.7% (range, 40-65%) in 9 patients.

Toxicity and Side Effects

[225Ac]Ac-DOTATATE administration was well tolerated. We did not observe any acute side effects, such as nausea or vomiting, during the injection. No change in blood pressure, fever, or pulse rate was not observed for 5 h in our patient group.

Before [225Ac]Ac-DOTATATE therapy, 4 of 11 patients had grade 1/2 hematologic toxicity and 2 of 11 patients had grade 1/2 nephrotoxicity. Toxicity analysis could be performed in 8 patients. Nephrotoxicity and grade 2 hematotoxicity were observed in one patient after 3 cycles of treatment with [225Ac]Ac-DOTATATE. The patient had received multistep chemotherapy and 13 cycles of [177Lu]Lu-DOTATATE before treatment with [225Ac]Ac-DOTATATE. The nephrotoxicity rate was 12.5% (n=1), and the hematotoxicity rate was 12.5% (n=1). A transient decrease in lymphocyte count was observed in all patients ($p<0.05$). The patients' WBC counts decreased but were still within the normal range ($p=0.02$). The mean values of WBC, PLTs, Hb, and hematocrit are shown in Table 2. One patient with peritoneal carcinomatosis required 7 days of hospitalization, intravenous fluid administration, and steroid treatment to control symptoms. None of the patients required discontinuation of treatment with [225Ac]Ac-DOTATATE because of adverse reactions.

The mean parotid maximum standardized uptake value (SUV_{max}) values were 2.98±0.96 before therapy (baseline), 2.07±0.93 after the first cycle (n=9), 2.48±0.59 (n=6) after two cycles of [225Ac]Ac-DOTATATE treatments. There was no statistically significant change in parotid gland uptake from baseline ($p=0.93$ after the first cycle and $p=0.73$ after the second cycle). Patients did not complain of xerostomia (Table 2).

Efficacy and Survival

According to [68Ga]Ga-DOTATATE PET/CT images three months after treatment (n=9), 44% of patients (n=4) showed a partial response (PR), 44% (n=4) showed stable disease (SD), and 11% (n=1) showed progressive disease. The disease control rate of treatment was 89% (n=8). In all patients (n=9), [68Ga]Ga-DOTATATE PET images and ceCT images interpreted according to the RECIST criteria yielded the same results ($p>0.05$). The median PFS estimated by Kaplan-Meier analysis was 12 months from the time of first treatment. The patient survival times are shown in Figure 3. PET images of the selected patients before and after treatment are shown in Figure 4.

Table 2. Hematological, renal, liver parameters and [68Ga]Ga-DOTATATE uptake of parotid glands before and after the last cycle of [225Ac]Ac-DOTATATE treatment*

	Before treatment	After treatment
White blood cells (cnt/µL)	6.94±4.09	4.09±2.34
Platelets (cnt/µL)	226.00±109.12	237.00±86.26
Hemoglobin (g/dL)	11.13±1.57	10.40±1.58
Hematocrit (%)	32.93±4.52	30.88±4.79
Creatinine (mg/dL)	0.86±0.44	1.16±0.41
Total bilirubin (mg/dL)	0.54±0.48	0.58±0.51
Albumin (g/dL)	3.90±0.72	3.84±0.74
Parotid gland (SUV_{max})	2.98±0.96	2.07±0.93

*$p>0.05$
SUV_{max}: Maximum standardized uptake value

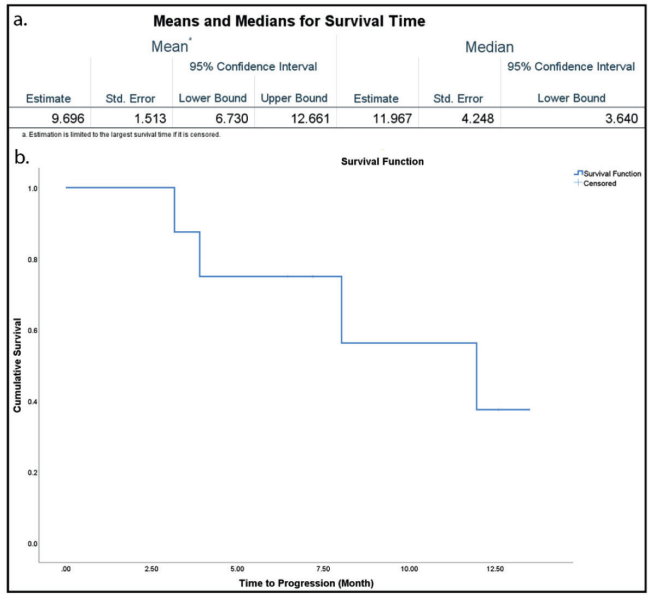

Figure 3. Kaplan Meier progression- free survival estimates **(a)** and patient progression-free survival curves **(b)**

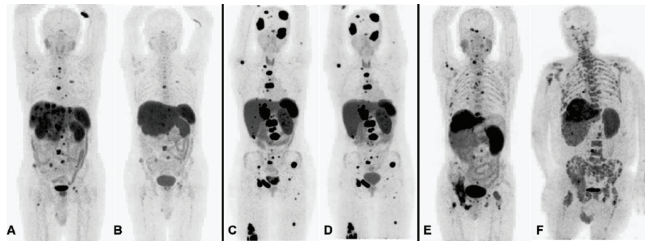

Figure 4. [68Ga]Ga-DOTATATE PET maximum intensity projection pre- and post-treatment images of selected patients with **A, B)** partial response, **C, D)** stable disease, **E, F)** progression
PET: Positron emission tomography

Discussion

There are limited treatment options for patients with metastatic NETs, especially after the failure of [^{177}Lu]Lu-DOTATATE therapy. Therefore, there is an urgent need for additional therapies for metastatic NETs. Targeted alpha therapies have several advantages over beta therapies, at least in theory. The most important finding is that high LET radiation has the ability to break DNA double strands and DNA clusters. In addition, alpha radiation isotopes are less dependent on tumor oxygen levels than beta radiation isotopes. These biological advantages may explain why TAT is superior to targeted beta therapy (15,19,20). Although [^{213}Bi] is only used in a limited number of patients, [^{225}Ac] is one of the leading alternatives to beta therapy (13,21). However, PRRT with [^{225}Ac]Ac-DOTATATE has not been clearly demonstrated in clinical trials. This study demonstrates the potential efficacy of [^{225}Ac]Ac-DOTATATE as an end-of-line treatment in patients who have experienced progression on therapy with [^{177}Lu]Lu-DOTATATE. According to our study, therapy with [^{225}Ac]Ac-DOTATATE may be a useful treatment option for patients with advanced metastatic NETs, increasing survival rates and providing disease management with few adverse effects. The disease control rate of 88.9% in our study is similar to the rates reported by Ballal et al. (22). In their report of 32 patients with NET treated with three cycles of [^{225}Ac]Ac-DOTATATE (100 kBq/kg), PR was 37.5% and SD was 62.5%. In a recent study of the same group, the disease control rate was 79.8% (23).

In our patient cohort, [^{225}Ac]Ac-DOTATATE therapy was generally well tolerated. Although patients were treated with intensive [^{177}Lu]Lu-DOTATATE and chemotherapy, none showed grade 3 hematotoxicity or nephrotoxicity. Grade 2 nephrotoxicity and hematotoxicity were observed in one patient after 3 cycles of treatment with [^{225}Ac]Ac-DOTATATE, who had previously been treated with intensive chemotherapy including cisplatin + etoposide and 13 cycles of [^{177}Lu]Lu-DOTATATE. Similar safety results have also been reported by Ballal et al. (22,23). In our study, none of the patients complained of xerostomia. SUV_{max} values before and after treatment with [^{225}Ac]Ac-DOTATATE showed no significant change. Tafreshi et al. (24) reported very low absorbed radiation doses in salivary glands in mice. Xerostomia does not appear to be a clinical problem in these patients. One patient who had not been previously treated with [^{177}Lu]Lu-DOTATATE required hospitalization 5 days after treatment with [^{225}Ac]Ac-DOTATATE for an ileus finding. The patient had received steroids to control her symptoms. This patient had an ileal NET and peritoneal metastasis. Strosberg et al. (25) reported 5 cases of bowel obstruction after treatment with [^{177}Lu]Lu-DOTATATE. All patients in this report also had ileal NETs and peritoneal metastases.

[^{225}Ac]Ac-DOTATATE had slightly decreased *in vitro* stability in saline, but the radiochemical yield was still higher than 96% after 5 h of incubation in saline. Thus far, DOTA has been shown to be the most suitable chelator for [^{225}Ac], but other studies have reported the loss of [^{225}Ac] from DOTA *in vitro* and *in vivo* (26,27). Because of rapid plasma clearance and volume distribution, stability in blood could be verified only 10 min after injection, and [^{225}Ac]Ac-DOTATATE remained stable in blood for up to 10 min. In urine samples, [^{225}Ac]Ac-DOTATATE remained stable for up to 3 h. More than half of the injected [^{225}Ac]Ac-DOTATATE was excreted by the kidneys 24 h after injection. However, organ dosimetry could not be performed because of the poor quality of the [^{225}Ac] whole-body images obtained 4 h after injection. It was not possible to delineate the organs although the kidneys had the highest physiological uptake of [^{225}Ac]Ac-DOTATATE (21).

This study has all the limitations of a retrospective design. The number of patients in this preliminary report is limited, and the results should be evaluated with caution. However, we believe that the results presented in this study are promising and that treatment with [^{225}Ac]Ac-DOTATATE appears to be a safe treatment option for patients who do not respond to treatment with [^{177}Lu]Lu-DOTATATE.

Conclusion

In conclusion, the results of the current study, together with the concordant literature, demonstrate that [^{225}Ac]Ac-DOTATATE is the treatment of choice and has a significant effect in patients with SSTR-2-positive metastatic NETs with high somatostatin receptor expression. Therapy with [^{225}Ac]Ac-DOTATATE did not cause significant toxicity in our heavily pretreated patient cohort. The preliminary results are very promising, and a multicenter randomized control trial of [^{225}Ac]Ac-DOTATATE therapy in NET patients is required.

Ethics

Ethics Committee Approval: This study was approved by the Yeditepe University Clinical Research Ethics Committee (decision no: 1633, date: 06.07.2022).

Informed Consent: Not applicable (retrospective study).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., N.A.S., G.B., M.O., K.A., Concept: E.D., N.A.S., L.K., Design: L.K., Data Collection or Processing: E.D., N.A.S., G.B., T.T., K.A., Analysis or Interpretation: E.D., N.A.S., T.T., Literature Search: E.D., N.A.S., L.K., Writing: E.D., N.A.S., T.T., L.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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