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Somatostatin Receptor-Directed Theranostics in Esthesioneuroblastoma

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Background: We aim to report on somatostatin receptor (SSTR)-targeted molecular imaging and therapy in patients with advanced esthesioneuroblastoma (ENB).

Patients and Methods: Five patients with ENB [Kadish stage D in 5/5 (100%); Hyams grade 2 in 2/5 (40%), grade 3 in 2/5 (40%), undetermined in 1/5 (20%)] underwent SSTR-directed PET/CT. We quantified SSTR-avid tumor volume (TV), maximum SUV (SUV_{max}), and target-to-background ratios (TBR). Based on imaging, peptide receptor radionuclide therapy (PRRT) along with dosimetry was also conducted. We recorded nephrotoxicity and hematotoxicity, including estimated glomerular filtration rate (eGFR), hemoglobin, leukocytes, and thrombocytes at baseline and after the last treatment cycle. We determined adverse events following Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Response and progression-free survival (PFS) was also evaluated.

Results: All 5 patients were rated positive on SSTR-PET/CT. On a lesion-based level, we identified 32 SSTR-avid tumor sites with a median TV of 11.7 ± 10.8 and SUV_{max} of 24.3 ± 12.8. TBR was 19.8 ± 9.7, indicating excellent image contrast. After median 4 (range, 2–6) cycles with a median of 7.7 GBq per cycle per patient, we observed no CTCAE grade 3 or 4 toxicity for leukocytes and thrombocytes and no significant CTCAE events for renal function. One patient (20%), however, developed reversible grade 3 anemia. Up to 11.8 Gy in tumor lesions were achieved. Partial response was recorded in 3/5 (60%), stable disease in 1/5 (20%), and progressive disease in 1/5 (20%). The median PFS was 29 weeks.

Conclusions: SSTR-directed PET provided high image contrast in ENB, suggesting good read-out capabilities in this tumor type. PRRT was also feasible, along with an acceptable safety profile, thereby rendering SSTR-targeted theranostics a potential treatment option in advanced disease.

Key Words: PET, PET/CT, SSTR, somatostatin receptor, ENB, esthesioneuroblastoma, [68Ga]Ga-DOTATOC

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Esthesioneuroblastoma (ENB) accounts for 0.4 per million inhabitants, thereby presenting ~2% of malignant sinonasal neoplasms.[1] As a common grading system upon initial diagnosis, the modified Kadish classification separates cases based on tumor extent, with A tumor limited to the nasal cavity, B involving paranasal sinuses, C extension beyond the nasal cavity/paranasal sinuses, and D lymph node involvement or hematogenic spread.[2] In this regard, higher stages are associated with poor outcomes, with Kadish A–C achieving a 5-year survival rate of 77%–88%, while for D, the respective rates showed a dramatic decline of up to 50%.[3] Another classification according to histopathologic findings was reported by Hyams, with Hyams grades 3 or 4 reflecting higher levels of necrosis and mitotic activity (5 and 10-y survival rates of 41%–61%).[4] As such, novel and innovative therapeutic approaches are intensively sought, in particular for aggressive disease.

Only early stages of disease (Kadish A, B) are restricted to surgical intervention, while for more aggressive disease (Kadish C), synergistic approaches of surgery and external beam radiation therapy led to improved outcomes. For distant involvement (Kadish D), however, therapeutic options are limited and included platinum-based chemotherapy in the vast majority of the cases, which did not

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The main data presented in this study are available in the article. Detailed information is available upon reasonable request from the corresponding author.

K.K. and M.A. contributed equally.

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achieve an improved survival relative to other chemotherapeutic strategies.[5] Of note, somatostatin receptor (SSTR) is overexpressed in sinonasal carcinomas, with the SSTR subtype SSTR2A in up to 75%, while SSTR subtype SSTR5 upregulation was recorded in ~7.5%.[6] Those subtypes, however, can be targeted in a theranostic approach using SSTR-directed molecular imaging [with (DOTA(0)-Phe(1)-Tyr(3))octreotid (^{68}Ga-DOTATOC) and DOTA-(Tyr^3)-octreotate (^{68}Ga-DOTATATE] followed by peptide receptor radionuclide therapy (PRRT).[7] In this regard, a previous case series of 7 subjects with ENB reported on the use of varying therapeutic radiotracers for SSTR-directed therapy, including the first-generation radiotherapeutic tracer ^{111}In-octreotate.[8] Given the more favorable benefit along with less toxicity profile in gastroenteropancreatic neuroendocrine tumor patients treated with ^{177}Lu-DOTATATE,[7,9,10] we aimed to provide a series of subjects affected with ENB, which were all imaged and diagnosed with second-generation SSTR-directed radiodiagnostics and therapeutics (^{68}Ga-/^{177}Lu-DOTATOC/-TATE). Moreover, relative to previous reports,[8] we also report on dosimetry in selected cases and provide information on outcome and toxicity profile.

PATIENTS AND METHODS

General

The local ethics committees did not require further approval given the retrospective nature of this study (waiver no: University Hospital Würzburg, 20231220 01). Patient data used in this study were provided by the University Cancer Center Frankfurt (UCT). Written informed consent was obtained from all patients and the study was approved by the Institutional Review Boards of the UCT and the Ethical Committee at the University Hospital Frankfurt (project-number: UCT-4-2024). Informed consent was obtained from all subjects involved in the study.

Patients

Five patients with several previous therapies (4 female, 1 male) between 57 and 68 years with histologic confirmed ENB [Kadish stage D in 5/5 (100%); Hyams grade 2 in 2/5 (40%), grade 3 in 2/5 (40%), undetermined in 1/5 (20%)] were included (Tables 1, 2). The patients reported on varying symptoms, which included partial vision loss or epileptical seizures from cerebral manifestations in 2/5 (40%) or neck pain due to lymphonodal cervical metastases in 1/5 (20%). Previous treatment regimens before PRRT included surgery and radiation (RTx) in 5/5 (100%). In addition, 2/5 (40%) chemotherapy and 1/5 (20%) antibody therapy were also performed before SSTR-directed therapy. During follow-up, we recorded progression-free survival (PFS) and overall survival (OS), defined as the time frame between the onset of PRRT and the date of image-based progression or death. Nephrotoxicity and hematotoxicity were also assessed, including estimated glomerular filtration rate (eGFR), hemoglobin, leukocytes, and thrombocytes at baseline and after the last treatment cycle. Classification of side effects followed Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[11]

Radiotracer Synthesis

^{68}Ga-DOTATOC was synthesized using a Scintomics synthesis module (Scintomics, Fürstenfeldbruck, Germany). ^{68}Ga-HA-DOTATATE was synthesized using an Elysia-Rayest synthesis module (Elysia S.A., Angleur, Belgium). The automated version of the Scintomics module employs sterile disposable cassette units from ABX (Radeberg, Germany) to facilitate GMP-compliant synthesis, for the Elysia-Rayest synthesis modules cassettes from ABX (Radeberg, Germany) were used, accordingly. The final quality control was conducted in accordance with Good Medical Practice, encompassing high-performance liquid, thin layer and gas chromatography, pH and sterility assessments as described in Hennrich and Benesova.[12] ^{177}Lu-DOTATATE was synthesized as described in Aslani et al.[13]

Imaging and Analysis

Before PRRT, every patient received ^{68}Ga-DOTATOC [n = 4 (80%)]/−TATE [n = 1 (20%)] PET/CT and with an average activity of 121 ± 27 MBq. Following a 60-minute period postinjection, imaging (including the entire body from the skull to the mid-thigh) was conducted using a Siemens Biograph mCT 128 in n = 4/5 (80%); for the remaining patient [n = 1/5 (20%)] a Siemens Biograph 6 (both, Siemens Healthineers, Erlangen, Germany) was used.

Two qualified nuclear medicine physicians with multiple years of experience in SSTR-directed scan interpretation conducted a comprehensive analysis of the PET/CTs, adhering to previous reports for quantification.[14] For each target lesion, a specific volume of interest (VOI) was delineated. Within these defined VOIs, the maximum standardized uptake value (SUV_{max}) was determined, providing a quantitative measure of SSTR expression intensity. To establish a reference, an additional VOI was positioned within the superior vena cava. The mean standardized uptake value (SUV_{mean}) was then extracted from this reference region. The target-to-background ratio (TBR) was then computed by comparing the SUV_{max} of each target lesion to the SUV_{mean} of the blood pool. Apart from providing the mean values and range of all sites of disease, we also conducted the hottest lesion analysis focusing on the tumor manifestation with the most intense uptake.

TABLE 1. Patient's Characteristics

Patient	Age	Sex	Hyams grade	Kadish grade	Therapy before PRRT	Symptoms before PRRT	Metastases before PRRT
#1	60	F	2	D	OP, RTx	Partial vision loss	Brain
#2	59	M	3	D	OP, RTx, CTx, AB	Sensation of pressure in the neck	Lung, LN
#3	57	F	2	D	OP, RTx	Epileptic seizures	Brain, LN
#4	58	F	3	D	OP, RTx	Epileptic seizures	Brain
#5	68	F	NA	D	OP, RTx, CTx	Asymptomatic	Brain, bone

Grading at time of PRRT on-set. Kadish grade was established right before PRRT. TNM classification was applied at the time of diagnosis.
AB indicates antibody therapy; CTx, chemotherapy; F, female; LN, lymph node; M, male; NA, not available; OP, operation; RTx, radiation.

TABLE 2. Details of Peptide Receptor Radionuclide Therapies (PRRTs) Including Toxicity and Outcome

Patient	Cycles of PRRT	Total cumulative activity	PRRT-related clinical/blood adverse events	Overall Imaging response to PRRT	PFS since PRRT (wk)
#1	6	47.6 GBq	None/grade 1 thrombocytopenia	PD	13
#2	4	30.8 GBq	Fatigue/none	PR	53
#3	4	31.2 GBq	Fatigue, sensory, and motoric disturbance in left leg/none	PR	36
#4	2	15.3 GBq	None/none	SD	20
#5	3	21.0 GBq	None/grade 3 anemia, grade 2 thrombocytopenia	PR	29

PD indicates progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease.

PRRT

PRRT was conducted using ^{177}Lu-DOTATOC [n = 4 (80%)]/−TATE [n = 1 (20%)] in accordance with current guidelines.[7] Vital signs were monitored during and immediately after treatment following standardized in-house workflows. Blood samples were collected at baseline and during follow-ups every 2 weeks to assess renal and hematological function. To evaluate long-term toxicity,

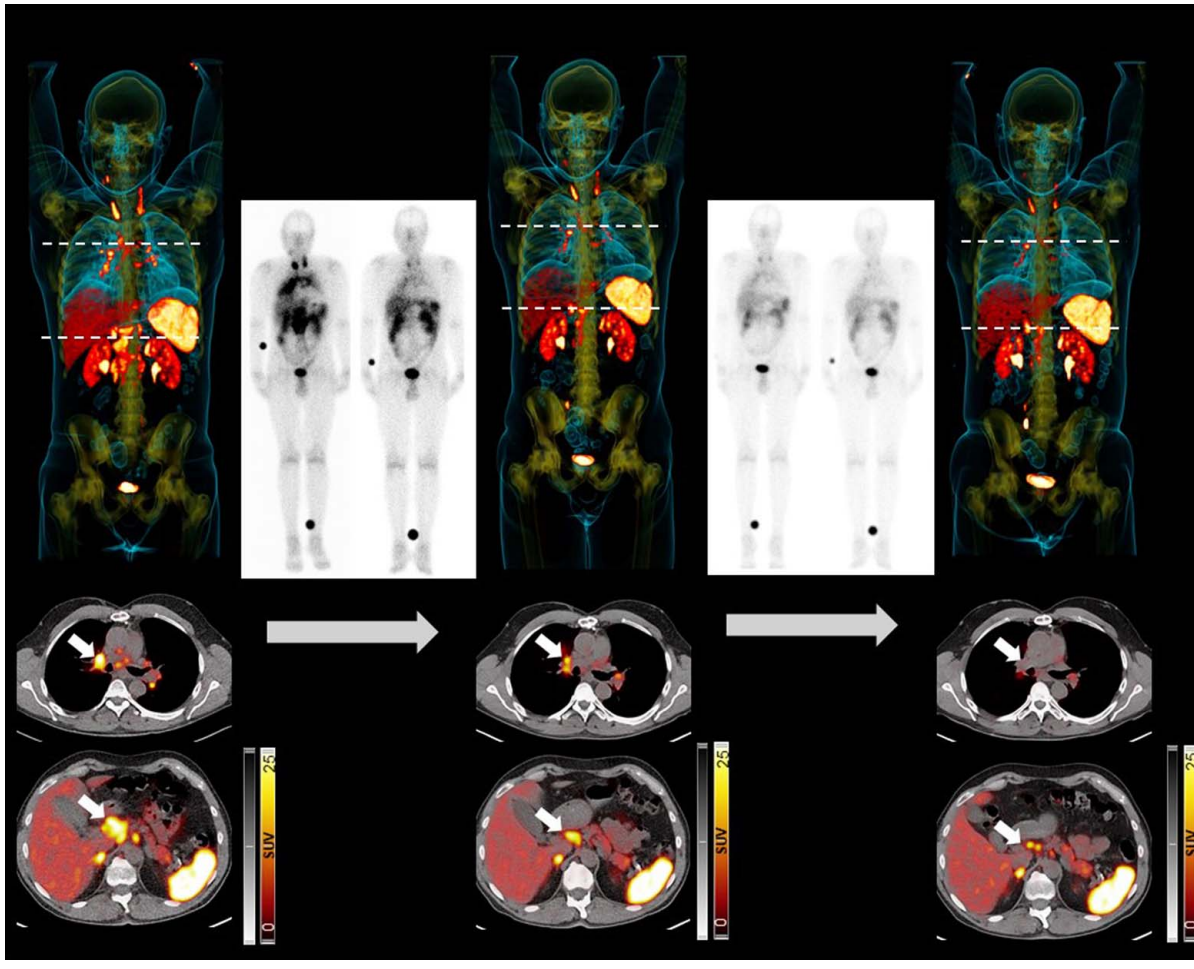

FIGURE 1. A 59-year-old man with esthesioneuroblastoma, classified as Kadish grade D and Hyams grade 3 with partial response upon first restaging (after 2 cycles of PRRT) and second restaging (after 2 more treatment cycles). Maximum intensity projections of SSTR-directed PET/CT and transaxial views are displayed on the left (at baseline before therapy), middle (restaging after 2 cycles of PRRT) and right (restaging after 2 more cycles). Posttherapeutic whole-body (WB) planar scintigraphy between restagings in the anterior views are also displayed (inserts). Left: at baseline, the patient presented with SSTR-positive pulmonal and lymph node lesions (arrows). Middle: after 2 cycles of PRRT, the patient showed partial response with a decrease in the size of lesions on SSTR-targeted PET/CT (arrows). Right: after 2 more cycles, the subject presented with a further decline of target lesions upon restaging with PET/CT (arrows). WB planar views right after the first and second cycles (insert, left) showed intense uptake after injection of the ^{177}Lu-labeled, SSTR-positive radiotherapeutic, which further decline of uptake after the third and fourth cycle (insert, right), which was most likely due to a decrease in tumor size under treatment.

laboratory values obtained before PRRT were compared with those from the last follow-up. Posttherapeutic dosimetry was conducted as described in Hanscheid et al,[15] with organ dose evaluation in 2/5 (40%) and tumor burden in 3/5 (60%). The response was determined based on follow-up SSTR-PET/CT and categorized as partial response (PR), stable disease (SD), or progressive disease (PD) following respective criteria.[16]

Statistical Analysis

We used Excel (2016) and GraphPad Prism (9.3; GraphPad Software, San Diego, CA) for descriptive statistics.

RESULTS

Pretherapeutic Imaging Provides Consistently Elevated In Vivo SSTR Expression and Image Contrast

Overall, 32 lesions (median, 6; range, 1–10) were identified. Organ involvement included the following compartments: brain, 12/32 (37.5%); lymph node (LN), 11/32 (34.4%); osseous structures, 4/32 (12.5%); lung 4/32 (12.5%) and primary, 1/32 (3.1%). Overall quantitative values in all lesions were as follows: median SUV_{max}, 24.3 (range, 4.7–37.0) and median TBR, 19.8 (range, 5.0–28.5).

The hottest lesion analysis focusing on the tumor site with the most intense uptake revealed the following results on a per-patient basis: LN and brain in 2/5 (40%), each and osseous lesion in 1/5 (20%). The median SUV_{max} in those lesions were 37.6 (range, 5.7–70.7).

PRRT Achieves High Absorbed Doses in Tumor Manifestations and Favorable Outcome Along With Manageable Toxicity

Median 4 (range, 2–6) cycles with 7.7 GBq per cycle were conducted. None of the patients reported any acute events and there were also no alterations in vital signs right after PRRT. After the end of treatment a SSTR-directed PET/CT was done. A median PFS of 29 weeks (range, 13–53 wk), while median OS was not reached as all patients were still alive at the date of censoring. The best response was PR in 3/5 (60%; Fig. 1). The further patients were SD in 1/5 (20%) and PD in 1/5 (20%). Posttherapeutic dosimetry revealed the following median absorbed doses at the end of treatment cycles: kidneys, 4.9 Gy; spleen, 4.0 Gy and liver, 0.6 Gy. In tumor manifestations, a median of 4.5 Gy (range 1.8–11.8 Gy) were achieved.

During follow-up, grade 1 and 2 thrombocytopenia occurred in 2/5 patients (40%). One patient developed grade 3 anemia 10 months after initiation of PRRT, which was reversible after administration of packed red blood cells.

DISCUSSION

In the present case series of advanced ENB patients homogenously imaged and treated with second-generation SSTR-directed radiotracers, we observed high in vivo receptor expression and TBR upon imaging, indicative for excellent read-out. In addition, in patients treated with PRRT using ^{177}Lu-DOTATOC/-TATE, we observed PR in 60% of the cases along with relevant PFS of 29 weeks upon follow-up. Moreover, all patients were alive on the day of censoring. The toxicity profile was also acceptable, with no renal toxicity. For hematology, there were only mild cases of grade 1 or 2 thrombocytopenia and one single individual developing reversible grade 3 anemia, thereby rendering SSTR-directed theranostics using ^{68}Ga/^{177}Lu-DOTATOC/-TATE as a promising therapeutic option in the end-stage ENB subjects classified as Kadish grade D.

As indicated by ex vivo reports investigating the SSTR expression on the ENB tumor cell surface,[6] imaging with revealed intense uptake in our study (hottest lesion SUV_{max}, 70.7), along with high TBR (~20-fold above bloodpool), thereby suggesting excellent diagnostic read-out capabilities. As an extremely rare disease,[1] the current literature on PRRT for treating ENB is also rather sparse and encompasses single case reports[17–19] or case series of consecutive subjects with extended disease.[8] Of note, those included varying nonuniform protocols with different SSTR-targeting radiotracers, such as the first-generation ^{111}In-octreotide[17] with or without ^{177}Lu-DOTATATE.[8] Such an approach, however, may limit therapeutic efficacy along with increased risk of side effects, including the development of myelodysplastic syndrome,[20] in particular after the administration of Indium-111. As such, current guidelines for PRRT in the context of SSTR-expressing gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) recommend the use of Yttrium-90 or Lutetium-177,[7] which have been advocated to achieve higher efficacy in tumor reduction along with the option of posttherapeutic scintigraphy due to the β- and γ-emission of the latter radionuclide.[7,15] These considerations are further reinforced by recently published promising results for aggressive GEP-NEN using ^{177}Lu-DOTATATE,[10] which will most likely allow a more widespread adoption of this therapeutic radiotracer in the clinic. Although the number of subjects in our study is rather small, the present report provides outcome and toxicity data on ENB patients treated with the currently most commonly used SSTR-directed radiotherapeutic agent applying a uniform protocol endorsed by current guidelines.[7,21] Moreover, we exclusively focused on end-stage Kadish D patients and observed substantial treatment response with PR or SD in 4/5 (80%; Fig. 1). In addition, treatment was well tolerated as no grade 4 renal or hematological events occurred during follow-up. These considerations of an acceptable toxicity profile were also confirmed by posttherapeutic dosimetry, which for the first time, provided absorbed doses to organs at risk in ENB patients treated with PRRT. For instance, the commonly applied renal threshold of 23 Gy was not exceeded in our cohort, which may provide further evidence that PRRT for end-stage ENB patients is well tolerated in a manner similar to GEP-NEN patients.[7,10]

A previous case report in ENB also demonstrated that SSTR-directed therapy using "hot" radiolabeled analogues may have the potential to facilitate debulking in a neoadjuvant approach.[19] Although none of our patients were scheduled for resection post-PRRT, the high rate of PR in our study may further highlight the need to investigate whether sequential algorithms of PRRT followed by surgery may allow to achieve a more durable response or even complete remission.[8] Moreover, such an approach may then also help to alleviate the broad range of symptoms caused by olfactory neuroblastoma, including vision loss due to the close proximity of the tumor to the optic nerve.[22] Moreover, relative to previous reports, none of our patients presented with deterioration due to preceding RTx,[8] also indicating that therapeutic algorithms before ^{177}Lu-based PRRT should be investigated in future studies, in particular as radiosensitizers.[23]

Our study has several limitations, including its retrospective character and the small number of subjects. Nonetheless, ENB is an extremely rare disease and thus, increasing patient numbers may be challenging to identify.[1] This, could be subject to future trials, for example, in (inter) national registries. Long duration until recurrence, however, renders PRRT as an alternative option in otherwise end-stage disease.[1] Thus, as presented in our case series, ENB patients with high tumor burden (Kadish D) may benefit from imaging and treatment with a uniform protocol using second-generation ^{68}Ga/^{177}Lu-labeled SSTR-targeted radiotracers endorsed by current guidelines.[7,21]

CONCLUSIONS

In the present case series, we report on end-stage ENB patients, which were scheduled for a uniform PRRT protocol following current guidelines. The herein observed benefit included excellent image contrast on SSTR-directed molecular imaging using ^{68}Ga-labeled compounds (TBR approximately above 20), followed by durable response after injection of ^{177}Lu-labeled SSTR-targeting radiotherapeutics (PR or SD in 80% of the cases).

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