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Case Report

Successful Combination of Olaparib and ^{225}Ac-Dotatate in a Patient with Neuroendocrine Tumor G3 and BRCA Mutation

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Keywords
Neuroendocrine tumor · Peptide receptor radionuclide therapy · BRCA mutation · Olaparib · Targeted alpha-particle therapy

Abstract
Based on the results of the NETTER-1 trial, peptide receptor radionuclide therapy with Lutetium-177 (^{177}Lu) – DOTATATE is authorized for the treatment of neuroendocrine tumors (NET) grade 1 (G1) and grade 2 (G2) of the intestine. After the failure of ^{177}Lu-DOTATATE therapy, targeted alpha-particle therapy (TAT) may be a possible treatment option. Here, we present a patient with cancer of unknown primary NET G2 later G3. The patient was referred to our hospital with urosepsis due to a second-degree urinary retention. After stent insertion, a contrast-enhanced computed tomography revealed a huge pelvic tumor without metastases. Initially, the patient had undergone surgical treatment. Later the patient developed liver metastasis and was treated by ^{177}Lu-DOTATATE therapy and four lines of systemic therapy. A disease progression was observed and with the knowledge of a germline BRCA1 mutation, the patient was treated with TAT (Actinium-225 [^{225}Ac]-DOTATATE) combined with olaparib. The patient achieved a significant treatment response for 12 months indicating that a combination therapy with an alpha emitter and olaparib demands further investigations in clinical trials.

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Introduction

In approximately 13% of patients diagnosed with neuroendocrine neoplasia (NEN), primary site of the tumor remains unclear. Treatment decision should be based on grading, functionality, somatostatin receptor status, tumor extent, and hepatic tumor burden [1]. The World Health Organization (WHO) 2019 classifications distinguish the heterogeneous G3 gastroenteropancreatic NEN into well-differentiated NET G3 and poorly differentiated neuroendocrine carcinomas G3 [2]. It was observed that patients with Ki67 <55% had a lower response (15 vs. 42%) and better survival (14 vs. 10 months) than patients with higher Ki67 ≥55% treated by platinum-based chemotherapy [3]. Despite missing data from phase 3 trials, different systemic therapies and peptide receptor radionuclide therapy (PRRT) are widely used treating NET G3 [4]. Here, we report the first case of a patient with a germline BRCA mutation and metastasized NET G3, who was successfully treated with a combination of a PARP-inhibitor (PARPi) and TAT.

Case Report

A 66-year-old woman was initially hospitalized to the emergency room with a fever of 38.7°C, hypotension and tachycardia in March of 2014. Laboratory tests showed elevated inflammation values, e.g., leukocytes 18.8 Gpt/L, CRP 405 mg/L and acute renal failure with a creatinine of 212 µmol/L and a glomerular filtration rate (GFR) of 20 mL/min/1.73 qm. A urine test showed leukocyturia, proteinuria, and plenty of bacteria. Ultrasound detected a horseshoe kidney and a second-degree urinary retention. In summary, an urosepsis was diagnosed. The patient was transferred to the intensive care unit and a stent insertion was performed. However, renal function remained restricted after intervention with a GFR of 60 mL/min/1.73 qm. The workup including a computed tomography (CT) of the chest, abdomen, and pelvis revealed a 10.5 × 10 × 11 cm inhomogeneous mass with cystic parts adjacent to the right ovary with contact to the right ureter, iliac vessels, bladder and suspicion of infiltration of the sacrum. Gastroscopy and colonoscopy were without result except for diverticulosis. A ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) showed no metastases. Initially, a sarcoma was histologically suspected. Therefore, the patient was treated with neoadjuvant radiotherapy followed by a tumor operation with iliac vascular and partial ureteral resection. The final histology revealed a NET G2 (Ki67 10%). Four months later, a CT scan showed two liver metastases. The patient refused further treatment at that time. Three months later, multiple liver lesions were detected with magnetic resonance imaging (MRI). A liver biopsy showed metastases of a well-differentiated NET G2 (Ki67 15%). A ^{68}Gallium (^{68}Ga) – DOTATATE PET showed intense somatostatin receptor expression in the liver lesions and in an additional focus close to the pancreas. Endosonographic ultrasound revealed a pathologic lymph node adjacent to the head of the pancreas but no tumor of the pancreas. In summary, we diagnosed a cancer of unknown primary NET G2.

Considering the slight renal impairment, the patient was treated with two cycles of dose-reduced ^{177}Lu–DOTATATE (3,669 and 4,057 MBq) and additional medication of lanreotide every 4 weeks. In the beginning this resulted in a disease stabilization. Six months after the second PRRT, the patient progressed and received everolimus with disease progression after 2 months. A further liver biopsy identified a NET G3 (Ki67 34%). Therefore, the patient was treated with 12 cycles of capecitabine plus temozolomide until progression. Another cycle of PRRT (4,747 MBq) achieved stabilization of disease. After additional 9 months, a progression occurred and the patient was treated with oxaliplatin and capecitabine. Significant dose

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reduction to a maximum of 60% due to fatigue and diarrhea was necessary and the chemotherapy was discontinued after 3 months for progression. A treatment overview is shown in Figure 1.

In April 2020, a molecular testing of the last liver biopsy via next-generation sequencing was initiated, as family history had revealed ovarian (mother), gastric (father), and colon cancer (2 paternal uncles). The analysis yielded a BRCA1 Mutation R691fs*10, tumor mutational burden zero, and microsatellite stability. A consecutive germline analysis confirmed the above-mentioned BRCA mutation as heterozygote germline mutation.

The patient started with Olaparib 200 mg twice daily 2 months after finishing the last chemotherapy. The tolerability was very good without any relevant side effects. Liver metastases remain stable. However, the tumor burden was large and the patient suffered from upper abdominal pain. Due to the known BRCA1 mutation, advanced disease, and limited treatment options, the patient was offered an individual medical treatment consisting of one cycle of PRRT with ^{225}Ac-DOTATATE (6.4 MBq, day 1) and Olaparib 100 mg twice daily (day 2–6) considering the renal insufficiency (GFR 40 mL/min/1.73 qm). The treatment was well tolerated without any relevant toxicity, e.g., haematotoxicity, and without further impairment of the renal function. Abdominal complaints disappeared. Olaparib was restarted with 200 mg twice daily 8 weeks after PRRT. Restaging with ^{68}Ga-Dotatate PET/MRI was performed 8 weeks, 5 and 8 months after PRRT, showing a significant decrease in the extended liver metastases (percentage change baseline to current: 28), see Figure 2. After 12 months, the large liver metastasis in the left liver lobe remained stable but a progression of smaller hepatic metastases in the right lobe was observed. An additional TAT in combination with olaparib was planned.

Discussion

Prognosis of NET G3 is limited with a median survival of 43.6 months [5]. To date, there are no approved treatment regimes for NET G3. Therefore, several prospective studies are ongoing to evaluate treatment options like PRRT, chemo- and immunotherapy as well as targeted therapies in NET G3 (NCT03972488, NCT04400474, NCT03351296, NCT02113800, NCT04524208).

Our patient initially had a well-differentiated cancer of unknown primary NET G2 that progressed to a NET G3 with a Ki67 of 34%. After PRRT and four lines of systemic therapy, there were only limited treatment options.

BRCA1 and BRCA2 mutations are associated with an increased risk, e.g., of the ovarian, breast [6], prostate [7] and pancreatic cancer [8]. BRCA mutations are common mutations causing homologous recombination repair defects (HRDs). PARPi, such as Olaparib, prevents the repair of single-strand breaks through multiple mechanisms resulting in the generation of DNA double-strand breaks during the replication process. These DNA damages cannot be repaired sufficiently in tumors with HRD and lead to increasing genetic instability and death of tumor cells [9]. PARPi are approved for the adjuvant, palliative or maintenance therapy in BRCA germline mutated tumors of the ovaries, prostate and breast. In pancreatic cancer with a germline BRCA1 or 2 mutation, maintenance with Olaparib after first-line platinum-based chemotherapy prolonged progression-free survival [10]. During the clinical course of our patient, a germline BRCA1 mutation was diagnosed. As already explained, this mutation causes a higher susceptibility for treatments, which causes DNA damage like radiation therapy. We decided to treat our patient with Olaparib in combination with TAT assuming that combining a DNA-repair modifying agent with TAT could enhance radiation efficacy. In preclinical data, it has been shown that

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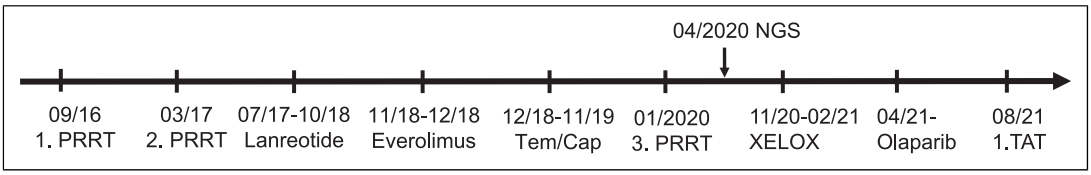

Fig. 1. Treatment overview. NGS, next-generation sequencing; Tem/Cap, temozolomide/capecitabine; XELOX, oxaliplatin/capecitabine.

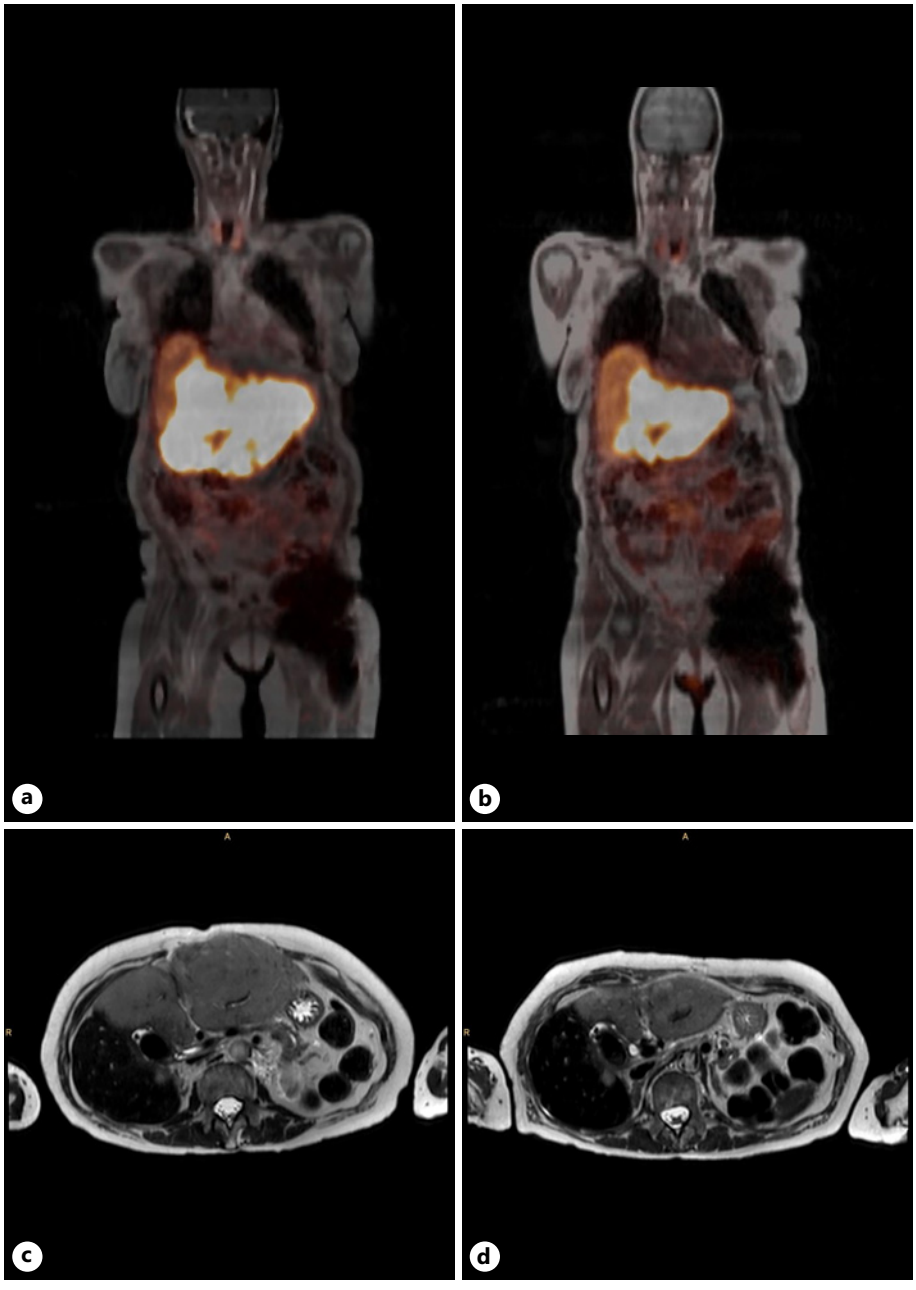

Fig. 2. PET/MRI. **a** PET/MRI fusion coronal June 2021. **b** PET/MRI fusion coronal March 2022. **c** Liver MRI T2-sequence June 2021. **d** Liver MRI T2-sequence March 2022.

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PARPi combined with PRRT enhances NET cell death and animal survival compared to PRRT alone [11, 12]. A patient with a pathogenic, heterozygous BRCA1 germline mutation was successfully treated with the beta emitter ^{177}Lu-DOTATATE [13]. Independent from HRD, the combination of PRRT and PARPi seems to be an interesting option to induce synthetic lethality and to enhance treatment efficacy. A study tried to optimize the treatment combination of PRRT and PARPi [14]. Two phase-1 studies PARLuNET for NET G2 (NCT05053854) and LuPARP for NET G2/G3 (NCT04375267) are ongoing to evaluate the feasibility and toxicity.

It is generally assumed that alpha emitters are more effective than beta emitters in tumor therapy since they have a higher linear energy transfer, resulting in more DNA double strand breaks and therefore causing more tumor cell damage than beta emitters [15, 16]. They are used as new radiopharmaceuticals, e.g., in the treatment of metastatic castration-resistant prostate cancer [17] and NET [18]. The combination of a PARPi with TAT, e.g. ^{225}Ac-DOTATATE, has the potential to enhance induced synthetic lethality through radiotracer-induced DNA damage. In this case report, we demonstrated a tumor shrinkage and a longer time to progression (12 months) with the combination of a PARPi and TAT than with ^{177}Lu-DOTATATE-based PRRT in the previous lines, which resulted in disease stabilization only, and in a shorter time to progression of 6–9 months. We assume that the interaction of PARPi with TAT contributed to the measurable and persistent response in this heavily pretreated patient. The treatment combination should be evaluated in further studies independently of an existing HRD in patients with NET after failure of ^{177}Lu-DOTATATE therapy.

We report the first case of a patient with a germline BRCA mutation and metastasized NET G3, who was successfully treated with a combination of a PARPi with TAT. The results support further research and prospective studies in this area. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533198).

Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local guidelines.

Conflict of Interest Statement

Anke Kröcher has received honoraria for lectures and/or ad-hoc advisory boards from IPSEN, Novartis and Servier. Gunnar Folprecht has received honoraria for lectures and/or ad-hoc advisory boards from Roche/Genentech, Merck KGaA, Sanofi, SMD, BMS, Servier, Pierre Fabre and had received an educational grant to the institution for a clinical trial from Merck KGaA. Martin Bornhäuser has received honoraria for lectures and/or ad-hoc advisory boards from Jazz Pharmaceuticals, MSD Sharp and Dome and Alexion.

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Author Contributions

Conception/design: A.K., C.B., and G.F. Provision of study material/patients: A.K., C.B., G.F., J.K., and M.B. Collection and/or assembly of data: A.K., C.B., R.W., and M.S. Manuscript writing: A.K., C.B., G.F., M.B., and M.S. Final approval of manuscript: all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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