Challenges in Von Hippel–Lindau's disease: PRRT in patients on hemodialysis

N Ayub[1], A J A T Braat[2], H J L M Timmers[3], M G E H Lam[2] and **R S van Leeuwaarde[1]**

[1]Department of Endocrine Oncology, University Medical Center Utrecht, Utrecht, The Netherlands , [2]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands, and [3]Departments of Endocrinology and Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence should be addressed to R S van Leeuwaarde
Email
r.vanleeuwaarde@umcutrecht.nl

Summary

Von Hippel–Lindau's disease (VHL) is a hereditary tumor syndrome characterized by its prototype lesions, hemangioblastomas, and renal cell carcinomas. Treatment for renal cell carcinomas can ultimately result in long-term dialysis. Pancreatic neuroendocrine tumors (pNET) can also occur in the course of the disease. Currently, peptide receptor radionuclide therapy (PRRT) is the standard treatment for progressive neuroendocrine tumors. However, little is known about treatment with PRRT in patients on dialysis, an infrequent presentation in patients with VHL. We present a 72-year-old man with VHL on hemodialysis and a progressive pNET. He received four cycles of PRRT with a reduced dose. Only mild thrombopenia was seen during treatments. The patient died 9 months after the last PRRT because of acute bleeding in a hemangioblastoma. Hemodialysis is not a limiting factor for PRRT treatment and it should be considered as it seems a safe short-term treatment option for this specific group.

Learning points:

- Von Hippel–Lindau disease (VHL) is a complex disease in which former interventions can limit optimal treatment for following VHL-related tumors later in life.
- Metastasized pancreatic neuroendocrine tumors occur as part of VHL disease.
- Peptide receptor radionuclide therapy seems a safe short-term treatment option in patients on hemodialysis.

Introduction

Von Hippel–Lindau disease (VHL) is an autosomal-dominant hereditary tumor syndrome that affects multiple organs. Major manifestations include the development of renal cell carcinoma (RCC), hemangioblastoma of the CNS, pheochromocytoma/paraganglioma, and pancreatic neuroendocrine tumors (pNET) (1).

VHL is caused by germline mutations located on the short arm of chromosome 3 and is a tumor suppressor gene that plays a vital role in the regulation of angiogenesis and cell division. The disease is highly penetrant with almost 100% of patients affected by the age of 60 (2).

Manifestations are often asymptomatic at early stages but can have severe sequelae, such as blindness, neurological complications, metastatic disease, or early death, if not diagnosed and treated appropriately. The estimated incidence of VHL is 1 in 39 000 (3). End-stage renal failure has been described in 23% of patients in a retrospective cohort series of VHL patients who underwent surgical treatment for renal cell carcinoma (4).

Mortality is mainly related to CNS hemangioblastoma accounting for 40% of deaths. However, another 30% of deaths are caused by renal cell carcinomas (5, 6). Pancreatic lesions occur in up to 70% of patients with VHL (7, 8). Pancreatic lesions are mostly cysts or serous cystadenomas but pNETs can be detected in 12–17% of patients with VHL (9). Although pNETs are an uncommon

cause of mortality they have malignant potential (8). In most cases, surgery is the primary treatment option. Besides local treatment, systemic treatment, such as peptide receptor radionuclide therapy (PRRT) with 71 Lutetium-177 (177Lu)-Dotatate is an option, for example, in case of metastatic disease (8).

PRRT (dilemmas and challenges)

The principle behind PRRTs efficacy is the dual component of the radiopharmaceutical. Firstly, the somatostatin receptor ligand that binds the specific receptor SSTR1-5 (especially SSTR2) overexpressed on the surface of neuroendocrine tumor cells, most commonly as an agonist, allows the internalization of the radiopharmaceutical into the tumor cells. Second, the high energy of the radioactive β-particle (yttrium-90 or 177Lu) labeled to a somatostatin receptor (SSTR) ligand yields cell apoptosis through, direct or indirect DNA damage of target cells (self-dose), or via neighboring cells (cross-fire effect). 177Lu is the most used isotope in PRRT (10).

PRRT has been proven to be an effective systemic treatment in the management of patients with advanced metastatic, or, inoperable slowly progressing NETs with high somatostatin receptor expression.

In a pivotal randomized phase 3 trial, 177Lu-DOTATATE was used for the treatment of progressive midgut neuroendocrine tumors. Treatment with 177Lu-DOTATATE resulted in longer progression-free survival than high doses of lanreotide. The rate of progression-free survival at month 20 was 65.2% compared to 10.8% in the control group (11).

Subsequently, other studies also confirmed improvement of the progression-free survival and overall survival (12, 13).

PRRT is associated with myelotoxicity and nephrotoxicity. Myelotoxicity can be short term or long term. Short-term toxicity is often reversible and is mostly limited to cytopenia (11). Long-term toxicity such as grade 3 or 4 has been reported to be as high as 9.5% (12, 14).

The risk factors for developing toxicities are the number of prior therapies, exposure to chemotherapy with alkylating agents, radiation-based therapy, receiving PRRT at ages 65 and above, impaired renal function; depleted myeloid reserve (manifesting as baseline cytopenias/ early development of significant grade toxicity, either due to bone marrow involvement or resulting from prior therapies), and poor performance status (14).

There is very little evidence on the effects of PRRT in hemodialysis patients. Currently, only two cases have been described. These patients were successfully treated with PRRT while on hemodialysis (15, 16).

Here, we describe the challenging case of a patient with VHL with progressive liver metastases of a pNET, who was successfully treated with PRRT while on hemodialysis after bilateral kidney resection due to multiple RCCs.

Case presentation

A 72-year-old man was referred to our academic hospital in June 2020 to consider PRRT for treatment of a progressive metastatic pNET (KI-67 1%). His medical history included VHL (p.Ser65Leu) with bilateral RCCs, requiring multiple surgeries eventually resulting in total nephrectomies in 2003. Following hemodialysis, he underwent kidney transplants in 2008 and 2009. Due to transplant failure, he restarted hemodialysis in 2016. He was on a three days a week dialysis scheme. Other VHL-related features were multiple cerebellar hemangioblastomas and pancreatic cysts.

In 2017, he developed liver metastases, histologically confirmed as a grade 1 neuroendocrine tumor and was started on a long-acting somatostatin analog. In 2019, a gallium-68 (68Ga)-DOTATOC PET/CT revealed multiple new liver metastases and progressive pre-existent liver metastases, despite treatment with lanreotide 120 mg monthly. After which he was considered to be a candidate for PRRT. Lanreotide was discontinued before PRRT.

Regarding the hemodialysis; out of precaution, the therapeutic PRRT activity was reduced by 50% (i.e. 3700 MBq), under the assumption that blood pool activity would be higher during the interval between the time of treatment and hemodialysis. This potentially would result in higher blood and bone marrow radiation absorbed dose and subsequently a higher likelihood to develop cytopenia. The PRRT was administered 1day after his hemodialysis and the following day he received the next hemodialysis. No amino acid infusion was performed (in absence of clinically relevant excretion by the native kidneys and to avoid potential hyperkalemia) and hemodialysis was performed in the nuclear medicine department the day before and the day after treatment. A mobile dialysis machine was used with completely disposable inserts.

All the materials used during hemodialysis were sterile disposables, and therefore, could be discarded according to local radiation safety regulations without the need to contain the machine itself. In total, he received four cycles of 3700 MBq 177Lu-DOTATATE with good tumor targeting (see Figs 1 and 2).
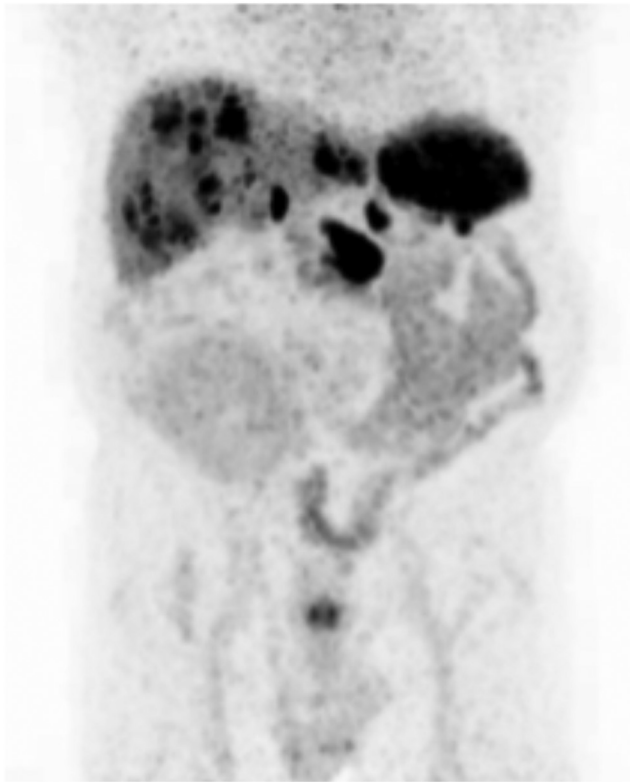
Figure 1
Pre-treatment tumor load maximum intensify projections of the GA-68-DOTATOC.

Besides a mild thrombopenia (90 × 10⁹/L) the bone marrow was hardly affected and he experienced no other side effects (see Figs 3, 4, 5 and Table 1). After four cycles, the disease was stable.

The disease status, according to RECIST, was assessed 6 months after the last PRRT. Besides some common mild fatigue problems, the patients experienced no additional side effects compared to non-dialysis patients treated with PRRT.

Unfortunately, in January 2021, a CT scan showed progression of the liver metastases and a high suspicion of peritonitis carcinomatosa.

Following a diminished performance status, he did not qualify for further systemic therapy. In March 2021, he died because of complicated bleeding in a hemangioblastoma.

Discussion

VHL is a complex multi-organ hereditary tumor syndrome. Treatment of a former VHL-related life-threatening tumor can potentially limit optimal treatment for following VHL-related tumors later in life.
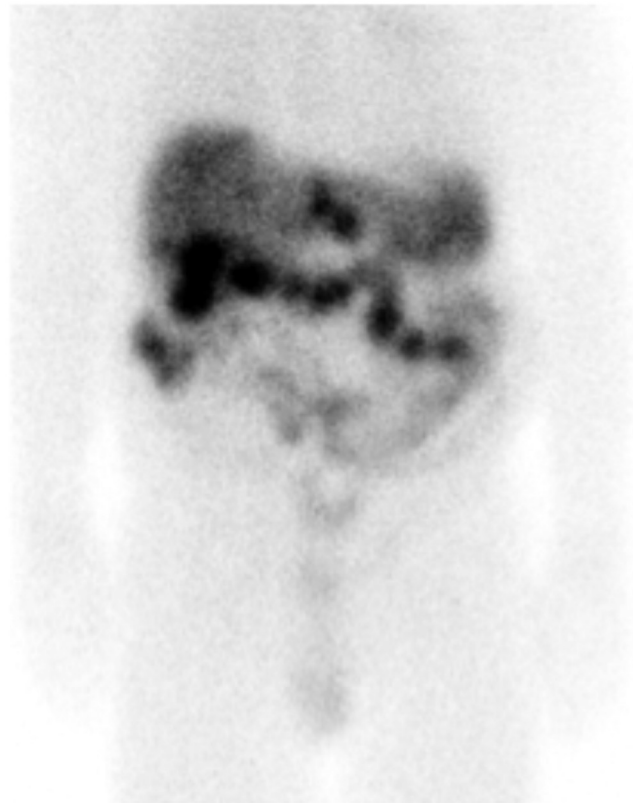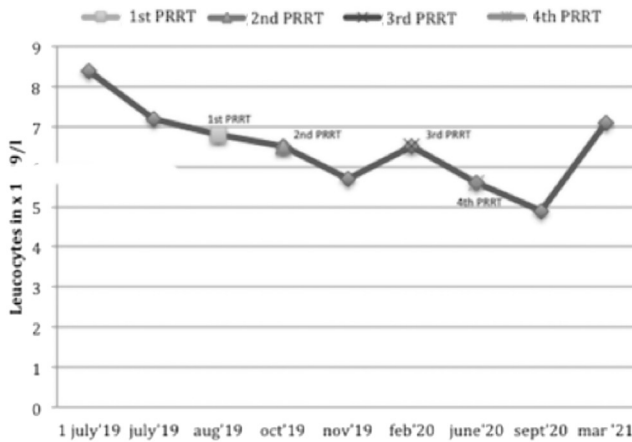

Figure 2
Post-treatment tumor load maximum intensify projections of the GA-68-DOTATOC..

In the current case, hemodialysis restricted the regular treatment dosage of PRRT. PRRT is predominantly but not exclusively cleared by renal excretion, which comes with another challenge in patients on dialysis.
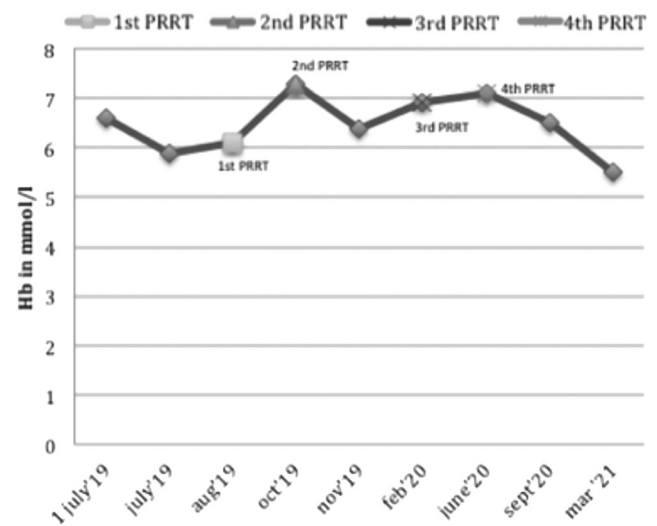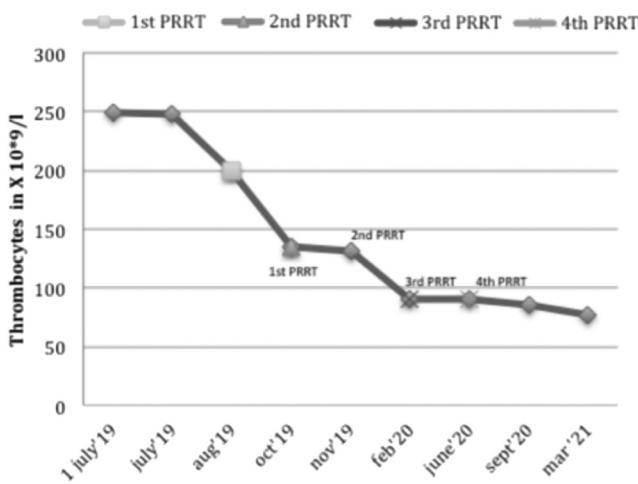

Figure 3
Hemoglobin levels and PRRT.

Figure 4
Leucocyte levels and PRRT.

Recommendations regarding preparation for treatment timing and follow-up are not specified for patients on hemodialysis.

Kalogianni *et al*. (16) assessed the individualized dosimetry to overcome this potential problem. In the case of Kalogianni *et al*. (16), a clinical decision was made to give 50% of the normal amount (i.e. 3700 MBq instead of 7400 MBq) in the first two cycles and a normal amount in the third. It has been suggested that the fraction of 177Lu-DOTATATE removed following dialysis decreases as more of the 177Lu-DOTATATE becomes bound to the receptors. The treatment plan consisted of three fractions of 177Lu-DOTATATE in a 15-month period. To prevent radiation exposure, the first dialysis was performed within 24 hours of therapy administration in all fractions.

In another reported case by Dierickx *et al*. (15), a 74-year-old woman on hemodialysis was successfully

Figure 5
Thromobocyte levels and PRRT.

Table 1 Pretreatment blood count values..

Baseline (July 2019)	(Reference values)
Hemoglobin	6.6 mmol/L (8.6–10.7 mmol/L)
Thrombocytes	249 × 10^9/L (150–450 10^9/L)
Leucocytes	8.4 × 10^9/L (4–10 10^9/L)

treated with PRRT. This patient was already treated with several other treatment modalities including three cycles of PRRT (yttrium-90 (90Y)-labeled once and 177Lu-labeled twice, with a cumulative activity of 20.5 GBq. Due to the relapse of the disease, a salvage PRRT was indicated. The second series was four cycles of 177Lu-DOTATATE with a cumulative activity of 18 GBq. She was in complete remission after 12 months and no side effects were reported (15).

The present case is in line with the previous cases regarding the observed toxicity, which is generally mild with an individualized dosimetry. Therefore, this treatment can be considered safe. Further treatment in our case was not possible because of the deterioration of his performance status due to VHL-related comorbidities.

Conclusion

In this report, we describe a patient with VHL on hemodialysis who was safely treated with four cycles of 3700 MBq 177Lu-DOTATATE for treatment of a metastasized pNET. PRRT was well-tolerated and was associated with mild thrombopenia. PRRT treatment for a short term seems to be safe for use in patients on dialysis.

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