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Peptide receptor radionuclide therapy as a tool for the treatment of severe hypoglycemia in patients with primary inoperable insulinoma

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Abstract

Objectives: Severe hypoglycemia in a course of inoperable insulinoma may be life-threating and often it is not well controlled, even by high doses of diazoxide requiring second line treatment. Among available methods PRRT is characterized by relatively low toxicity and is connected with favorable antitumor effect. The aim of the study was an evaluation of the PRRT effectiveness in control of hypoglycemia in patients with primary inoperable insulinoma.

Methods: Three patients (female with metastatic insulinoma, male with primary inoperable pancreatic tumor, female with MEN1 syndrome and hepatic metastases) were treated with PRRT due to severe hypoglycemia poorly controlled by diazoxide in course of primary inoperable insulinoma.

Results: Patient 1 baseline fasting glucose concentration increased from 2.4 mmol/L [3.30–5.60] to 5.9 mmol/L after PRRT. In patient 2 fasting glucose level 2.30 mmol/L increased after PRRT to 7.0 mmol/L, while baseline insulin level initially 31.15 uU/mL [2.6–24.9] decreased to 15.4 uU/mL. In patients 3, baseline fasting glucose level 2.5 mmol/L increased after PRRT to 7.9 mmol/L, and insulin decreased from 57.9 uU/mL to 6.3 uU/mL. In imaging there was partial response (PR) in patient 1 and 2 and stabilization of the tumor size in patient 3. In patient 2 reduction of tumor infiltration let for curative surgery performed 4 months after PPRT.

Conclusions: PRRT may be effective as a first or second line treatment in management of hypoglycemia for patients with hormonally active inoperable insulinoma.

Keywords: diazoxide; hypoglycemia; insulinoma; NET; neuroendocrine tumors; PRRT.

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Introduction

Insulinomas are rare neuroendocrine tumors (NETs), with an estimated incidence of 1–32 cases per million yearly [1]. They are found almost exclusively in the pancreas (PanNETs). Usually insulinomas are diagnosed as sporadic tumors, but in about 10% of cases they are the part of an inherited syndromes, mainly multiple endocrine neoplasia type 1 (MEN-1) (<5%) and less frequently von Hippel–Lindau disease (VHL), tuberous sclerosis complex and neurofibromatosis type 1 [2]. Most of them are benign, but the malignant ones constitute about 10% of cases and are more frequently connected with hereditary syndromes.

The clinical picture of insulinoma may be revealed by the presence of Whipple's triad, which denotes severe hyperinsulinemic hypoglycemia, which often occurs on fasting or after exercise, resolving after carbohydrate administration. The diagnose of insulinoma follows a spontaneous or occurred during a fasting test episode of hypoglycemia accompanied by not adequately high levels of proinsulin, C-peptide or insulin [1]. However, hypoglycemia is a main sign of insulinoma, the low blood glucose level alone is insufficient to its diagnose. Moreover, absolute insulin level elevation without hypoglycemia may be seen in cases of different hyperinsulinemic syndromes not connected with insulinoma. Differential diagnosis of insulinoma should include oncological disorders connected with hypoglycemia such as big-IGF-2-producing tumors, liver failure, glycogen storage diseases, nesidioblastosis and overdosing of exogenous insulin or sulfonylureas.

Localization of an insulinoma can be challenging. The effectiveness of basic diagnostic procedures is summarized in Table 1 [3]. Some of those techniques especially somatostatin

receptor imaging (SRI) may determine treatment options. SRI in PanNET is used as the method of choice in the initial clinical staging, diagnosis of early relapse, disease monitoring, and therapeutic decision making. In selected cases, it is possible to use intraoperative imaging of somatostatin receptors (SSTR). The method is useful in imaging of the primary lesion and searching for metastases to the locoregional lymph nodes, significantly facilitating an operation [4]. In some centers imaging of glucagon-like peptide-1 (GLP-1) receptors is also possible [5].

Because most insulinoma tumors are small (<2 cm) and benign usually surgical approach results in a high cure rate (98–100%) and, if possible, it is the first choice treatment. In some cases the use of ablative therapy with radiological guidance done endoscopically or percutaneously ablation has been also found successful in insulinoma treatment [6, 7].

In case of primary unresectable or metastatic insulinoma, palliative surgery should be considered. There are studies proving longer overall and progression free survival (PFS) after primary tumor removal, although it is usually connected with little improvement in symptomatic control of hypoglycemia.

In case of insulinoma, hypoglycemia can pose a significant clinical risk increasing mortality and lowering quality of life. For that reason in perioperative period and in case of unresectable or metastatic insulinoma some conservative treatment is necessary. Usually frequent small meals and diazoxide can manage hypoglycemia [8], however, in the case of malignant insulinomas, such management is rarely effective enough. Diazoxide therapy may be supported with hydrochlorothiazide, which prevents hyperkaliemia and edema at the same time increasing the hyperglycemic effect of diazoxide. Sometimes corticosteroids, including prednisolone, may also be effective for patients presenting refractory hypoglycemia. Unfortunately, in patients with malignant insulinoma usually there is a necessity for the use of another treatment regimen. Next steps may include use of somatostatin analogs, loco-regional treatment, kinase inhibitors or peptide receptor radionuclide therapy (PRRT). Those regiments bring additionally antiproliferative effect prolonging PFS and overall survival (OS) [1]. According to the literature, approximately 50% of patients with insulinoma respond to somatostatin analogs (SSA). Patients starting SSA need careful monitoring due to increased chance of aggravation of hypoglycemia. SSA may attenuate the compensatory effect of glucagon and lead to worsening of hypoglycemia [9]. Some previous studies demonstrated that everolimus, which is the mammalian target of rapamycin (mTOR) inhibitor, can be effective in controlling hypoglycemia by reduction of insulin secretion and increase of insulin resistance. Temozolomide based chemotherapy, PRRT or locoregional treatment like chemoembolization or Radio Frequency Ablation (RIA) can also control hypoglycemia [10]. Nevertheless, due to the rarity of the disease, there are only small series of patients with malignant insulinoma published comparing different methods of treatment.

The main goal of the study was a retrospective evaluation of the PRRT effectiveness in control of hypoglycemia in patients with primary inoperable insulinoma unsuccessfully treated with diazoxide.

Table 1: Sensitivity of different techniques of insulinoma imaging [3].

Radiology three phase CT	**Sensitivity 60–80%**
MRI (T1 + T2 weighted images + fat suppression)	85–90%
Endoscopic ultrasound (EUS)	75–90%
Arterial calcium stimulation – venous sampling	80–90%
Intraoperative localizing techniques	
Palpation	70%
Intraoperative ultrasound (IOUS)	75–90%
Palpation plus IOUS	85–95%
Nuclear medicine	
Somatostatin receptor imaging SPECT/PET	46–50%/ 50–86%
18F-DOPA PET	50%
Glucagon-like peptide-1 (exendin-4) receptor imaging SPECT/PET	75/95%

Materials

Three patients with primary inoperable insulinoma (patient 1: female aged 58 with insulinoma and metastases to liver, patient 2: male aged 42 with primary inoperable tumor of pancreatic head, patient 3: female aged 25 with MEN 1 syndrome and hepatic metastases) having repeating episodes of hypoglycemia despite high doses of diazoxide were treated with PRRT. The clinico-pathological characteristics of the patients are summed up in Table 2.

Methods

Three patients previously not treated ontologically were qualified to PRRT due to repeating episodes of hypoglycemia despite high doses of diazoxide. Eligibility criteria and treatment scheme followed the joint IAEA, EANM, and SNMMI recommendations of practical guidance on PRRT in NETs [11]. All of the patients before PRRT were in good general

Table 2: The clinico-pathological characteristics of each patients.

	Patient 1	Patient 2	Patient 3
Gender	F	M	F
Age at diagnosis, years	58	42	23
24 h fasting test	Positive	Positive	Positive
Insulin at diagnosis, µUI/mL	18.0	31.2	57.9
Glycemia at diagnosis, mmol/L	2.4	2.3	2.5
Site of NET in pancreas	Head	Head	Head
WHO grading of NET	G2	G2	G2
NET diameter, mm	20	43	30
Distant metastases, at PRRT	Liver, lymph nodes	None	Liver
Insulin staining	Negative	Positive	Positive
Time from the symptoms onset to diagnosis, months	3	2	2
Genetic syndrome	No	No	MEN1 (hyperparathyroidism at the moment of insulinoma diagnosis)
Family history	No clinical relevance	No clinical relevance	No clinical relevance

condition (Karnofsky index over 70%) and had positive result (Krenning score 3, 4) of SRI ([99mTc]Tc-EDDA/HYNIC octreotate SPECT/CT or [68Ga]Ga-DOTA-TATE PET/CT) The radiopharmaceuticals [90Y]Y and [90Y]Y/[177Lu]Lu-DOTATATE was prepared using 90Y and 177Lu (ItraPol, LutaPol) according to manufacturer's recommendations (POLATOM, Poland). All of patients received PRRT (in the dose 7.4 GBq/m^2), one 11.84 GBq (320 mCi) of 90Y-DOTA-TATE, two 90Y/177Lu-DOTA-TATE 14.8 GBq (400 mCi) in four cycles and 18.5 GBq (500 mCi) in five cycles, respectively. The intervals between PRRT cycles ranged 4–10 weeks. Their lengths depended on PRRT schemes, which were up-dated in our center over the years and radiopharmaceutical availability in particular time frames. There were no clinically significant hematological or renal toxicity which required the postponement of consecutive treatment cycles.

In order to reduce the radiation dose to the kidneys, as recommended [11], an infusion of amino acids (Vamin-18, Fresenius Kabi) was administered intravenously. Vamin-18 was administered in a total volume of 1,500 mL (on the day of PRRT 1,000 mL, starting 2 h before PRRT injection, on the next day after PRRT 500 mL). The infusion of Vamin-18 was preceded by the intravenous administration of an antiemetic drug (ondansetron 8 mg [Atossa, Anpharm SA]) to prevent nausea and vomiting.

Routine blood count, kidney and liver function were assessed before each therapy cycle and at follow-up visits. Glucose and insulin level were assessed before qualification to PRRT and after PRRT completion.

Results

In all patients, PRRT had no complications, but all of them required glucose monitoring and intravenous glucose injection. In a patient 1 baseline mean fasting glucose level was 2.4 mmol/L [3.30–5.60] and increased to 5.9 mmol/L after completing of PRRT. It allowed to maintenance of hypoglycemia on two tablets of diazoxide per day. In patient 2 mean fasting glucose concentration 2.30 mmol/L increased after PRRT to 7.0 mmol/L. Baseline insulin level initially 31.2 uU/mL [2.6–24.9] after PRRT decreased to 15.4 uU/mL what allowed for discontinuation of diazoxide. In female patients, baseline fasting glucose level mean 2.5 mmol/L increased after PRRT to 7.9 mmol/L, and insulin decreased from 57.9 uU/mL to 6.3 uU/mL which allowed to reduce diazoxide dose from 6 to 2 tablets a day (Figures 1 and 2). Symptomatic response was associated with good radiological response in all three patients (Table 2). All patients observed improvement in QoL after PRRT especially due to the reduction of severe hypoglycemia episodes. The radiopharmaceuticals type, dose,

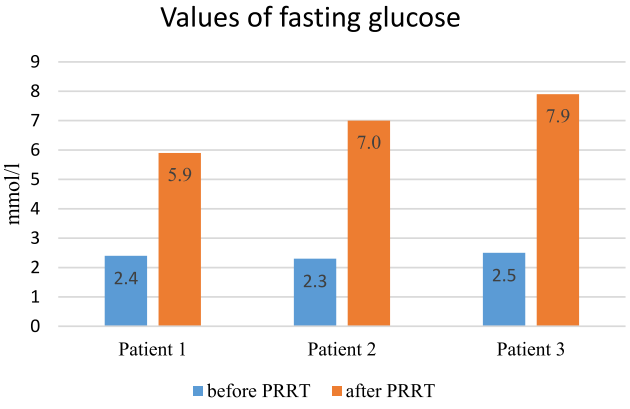

Figure 1: Values of fasting glucose before and after PRRT.

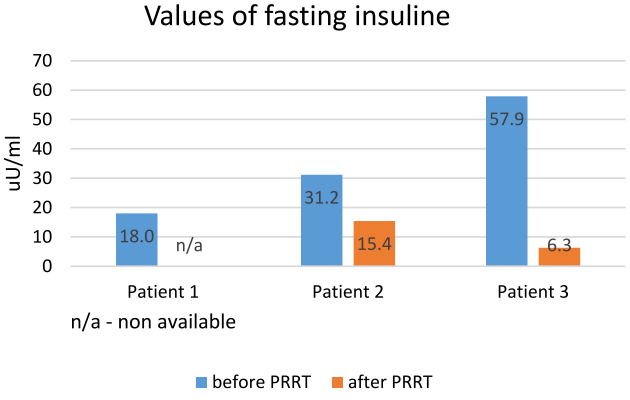

Figure 2: Values of fasting insulin before and after PRRT.

results of PRRT assessed in RECIST scale as well as kidney, liver and bone marrow parameters before and after PRRT in each of patients are summarized in Table 3.

Discussion

Although there are several potential options for the management of hypoglycemia caused by insulinoma there is a scarce data supporting best approach in case of inoperable tumors. In limited cases malignant tumors can be treated surgically especially if localized or oligometastatic disease is present. Patients with high tumor burden may benefit from debulking surgery or liver directed therapy. Those therapies even not curative may be effective in decreasing the severity of hypoglycemia. However, most malignant, metastatic insulinomas require concomitant conservative management. Among conservative methods an increasing doses of octreotide/lanreotide in refractory cases can be of value as well as use of pasireotide which is a second generation of SSA [12]. Other possibilities include control of the insulinoma symptoms by using targeted therapy: mainly the mammalian target of mTOR inhibitor (everolimus) or PRRT. Data in regard to sunitinib use are not unequivocal [13, 14]. It is worth remembering that insulinoma may be the first clinical manifestation of mutations in MEN 1 syndrome [15].

The diversity of NETs including PanNETs and insulinoma can lead to a different treatment effect in patients who appear similar at the initial disease stage. In regard to different malignancies more and more studies concern the use of various parameters obtained in molecular imaging for prediction of response to treatment [16]. This is particularly important in the case of NETs, where high heterogeneity of tumors may appear both within a single lesion and between different disease foci [17]. A choice of malignant insulinoma therapy requires not only taking into account hypoglycemia management, but also should take into consideration its impact on tumor growth and risk of side effects. In such comparison, PPRT seems to be the most effective, however, it can be used only in patients with the positive result of SRI.

A recent meta-analysis including 18 publications assessed the sensitivity and specificity of SRI in PanNET patients at 79.6% (95% CI: 71–87%) and 95% (95% CI: 75–100%), respectively, and primary focus detection rate at 81% [18]. The exception is insulinoma, where overexpression of SSTR is found in 50–60% of cases [19]. According to literature, the frequencies of expression of different SSTR types in insulinoma are: SSTR1 – 51%, SSTR2 – 69%, SSTR3 – 62%, SSTR4 – 39%, SSTR5 – 66% [20] causing 68Ga-DOTA-peptides PET/CT less effective in diagnosis in comparison with other PanNETs. The glucagon-like peptide 1 receptor (GLP-1R), which is mainly expressed on the pancreatic beta cells, is proved as an effective imaging target of mainly benign insulinomas [5, 21, 22]. On the contrary to benign insulinomas, malignant ones do not express GLP1-R, but they more often present a high somatostatin analog uptake [23] enabling use of PRRT. This therapy is generally safe, well-tolerated, and effective in the treatment of disseminated NET patients with disease control rates around 80%. The main complication of PRRT in insulinoma patients may be acute aggravation of hypoglycemic symptoms during or after

Table 3: The summary description of each patient's PRRT results.

	Patient 1	Patient 2	Patient 3
Type of PRRT	90Y-DOTA-TATE	90Y/177Lu-DOTA-TATE	90Y/177-Lu-DOTA-TATE
Number of PRRT cycles	4	4	5
Cumulative doses of PRRT, mCi/GBq	320/23.7	400/29.6	500/37.0
Insulin after PRRT, μUI/mL	n/a	15.4	6.3
Glycemia after PRRT, mmol/L	5.9	7.0	7.9
Hemoglobin level before and after PRRT, g/dL	12.5/9.4	14.2/14.2	11.8/10.6
White blood cells count before and after PRRT, 10^3/μL	7.9/5.6	5.4/3.4	11.2/4.8
Platelet blood count before and after PRRT, ×10^3/μL	394/203	413/200	991/345
Creatinine level before and after PRRT, umol/L	62.3/59.7	84.0/94.0	59.0/65.0
Alanine aminotransferase before and after PRRT, mmol/L	75.0/62.0	49.0/25.0	11.0/13.0
Response in imaging after PRRT	PR	PR	SD
Clinical improvement after PRRT	Significant	Significant	Significant
PFS after PRRT, months	6	Radical surgery after PRRT	15
Follow-up after PRRT	OS – 12 months	Full remission To date–29 months	Alive, 30 months

PR, partial response; SD, disease stabilization; n/a, non available.

PRRT. Usually diazoxide with continuous intra venous infusion of glucose are sufficient to prevent severe hypoglycemia during PRRT.

There is little evidence and experience of PRRT use in case of primary inoperative insulinoma with severe hypoglycemia, refractory to traditional treatment with high doses of diazoxide [24]. We present three cases in whom PRRT was used as a first line (after diazoxide failure) treatment. In all reported patients PPRT treatment showed efficacy in control of severe hypoglycemia. In case of patient 2 reduction of tumor infiltration let for curative surgery, in patients 1 and 3 for stabilization of the disease. Our data encourage the previous results from several retrospective studies indicating the role of PRRT in relieving symptoms of hypoglycemia. The largest published study summarizing efficacy of 177Lu-DOTATATE in functioning PanNETs patients showed encouraging results of symptomatic and biochemical response in a high percentage of patients treated with PRRT. Specifically, in 14 insulinoma patients there was a decrease of hypoglycemic events in 67% of cases, but degree of fasting glucose and insulin change was not provided [25]. Another study including also 14 insulinoma patients treated with PRRT as second or further line treatment showed good clinical outcome including hypoglycemia management. In this study PRRT used as second-line treatment was connected with a better prognosis than in cases when PRRT were used in further treatment lines, although the 5-year OS was not statistically different [13]. This study also confirmed that Ki-67 was an independent prognostic factor of OS as well as a level of serum insulin. Additionally, it showed a trend toward higher insulin levels in patients with G2 and G3 PanNETs in comparison with patients with G1 NETs [13].

Most of the presented reports showed that mean PFS and OS after PRRT is longer in comparison with results of the use of everolimus (mTOR inhibitor) and high doses of SSA. The RADIANT-03 trial which demonstrated everolimus improving PFS from 4.6 months with placebo to 11 months in the estimated risk of disease progression in patients with advanced PanNETs [26]. PRRT was approved as a parallel approach for PanNET, in addition to small bowel NET, after the NETTER-1 trial. In those trial longer PFS and OS was found in PRRT group in comparison to group treated with high dose of somatostatin analog octreotide [27]. A joint analysis of the published two prospective and six retrospective studies using PRRT in PanNETs was established the median PFS ranging from 20 to 39 months and the median OS from 37 to 79 months [28]. However, the use of PRRT in case of unresectable insulinoma is connected with rather shorter PFS an OS in comparison of PRRT used in all PanNETs cohort [25]. In our material PFS in non-operated patients PFS was 6 and 15 months, respectively, and was significantly shorter than in general group of metastatic PanNET undergoing PRRT.

Summarizing, in the line with other studies, our data showed that the use of PRRT in selected primary unresectable insulinoma should be considered as an effective therapy in controlling hypoglycemia. This therapy improves quality of life and cause clinically important stabilization of the disease. According to our data in some cases PRRT should be considered as neoadjuvant/first-line treatment bringing favorable effect in control of severe hypoglycemia.

Conclusions

- In case of unsuccessful surgical treatment of insulinoma there are several therapeutic modalities such as diazoxide, mTOR inhibitors, pasireotide, PPRT which can be used to control hypoglycaemia, but most of them are connected with significant side-effects.
- Although benign insulinomas usually express a low number of somatostatin receptor type 2, malignant insulinoma more frequently possess a higher somatostatin analog uptake enabling the use of PRRT.
- Among all available treatment methods PRRT seems to be valuable in inoperable insulinoma management due to its high effectiveness, safety and relatively good profile, enabling PRRT use as first or second line treatment (after diazoxide failure or intolerance).

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