Case Report · Kasuistik

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Peptide Receptor Radionuclide Therapy (PRRT) in a Patient Affected by Metastatic Breast Cancer with Neuroendocrine Differentiation

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Summary
Background: Breast cancer (BC) is the most frequent cancer in European women with nearly 30% of the patients eventually developing metastases. Neuroendocrine differentiation is a rare event, but overexpression of somatostatin receptors in BC has been reported in many studies. **Case Report:** A patient with liver metastases from BC was treated with peptide receptor radionuclide therapy (PRRT). Computed tomography scan and biochemical examinations showed a clear response to radionuclide therapy. **Conclusion:** PRRT may be useful in metastatic BC patients.

Schlüsselwörter
Radionuklidtherapie · Peptidrezeptoren

Zusammenfassung
Hintergrund: Das Mammakarzinom ist die häufigste Krebserkrankung bei Frauen in Europa, und ca. 30% der Patientinnen entwickeln schließlich Metastasen. Eine neuroendokrine Differenzierung ist selten. Die Überexpression von Somatostatin-Rezeptoren beim Mammakarzinom wurde jedoch in vielen Studien beobachtet. **Fallbericht:** Eine Patientin mit Lebermetastasen eines Mammakarzinoms wurde mit Peptidrezeptor-Radionuklidtherapie (PRRT) behandelt. Die computertomographische and biochemische Untersuchung zeigte ein deutliches Ansprechen auf die Radionuklidtherapie. **Schlussfolgerung:** PRRT könnte bei der Behandlung des metastasierten Mammakarzinoms hilfreich sein.

Introduction

Breast cancer (BC) with neuroendocrine differentiation (NED) is a rare neoplasm. Tables 1 and 2 show, respectively, the most important locations of neuroendocrine tumors and their World Health Organization (WHO) classification. Many studies have reported overexpression of somatostatin receptors (SSTR) in primary BC both in vitro and in vivo [1–8], whereas fewer analyses have evaluated their pattern in BC. Many authors do not consider evidence of SSTR overexpression alone to be sufficient to define an NED and stress the importance of neuroendocrine markers such as chromogranin and synaptophysin. The prognostic factors resulting from NED in BC are still a matter of debate with some researchers suggesting that BC with NED is a unique clinicopathologic entity with a poor outcome [9, 10], whereas others maintain a more open approach [11].

Case Report

In December 2007, a 52-year-old woman with liver involvement from BC presented to our hospital for treatment. The patient had a history of BC of the left breast diagnosed in March 2003 and was treated according to commonly accepted clinical guidelines, i.e. quadrantectomy and axillary

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node dissection. Pathology showed ductal infiltrating carcinoma with NED, positive for estrogen and negative for progesterone and c-ERB receptors. 1 cycle of adjuvant external beam radiation therapy was carried out, followed by tamoxifen which was substituted with anastrozole and triptorelin for intolerance. This schedule was considered to perform a complete estrogen blockade in this perimenopausal patient and prevent a potentially detrimental effect of anastrozole on residual ovarian function (despite amenorrhea).

In June 2006, a computed tomography (CT) scan showed evidence of 3 liver metastases which were confirmed to be derived from BC by biopsy. Immunohistochemistry showed synaptophysin and chromogranin, strengthening the diagnosis of NED. Chemotherapy with docetaxel and epirubicin was carried out and achieved a radiological partial remission. In July 2007, a CT scan showed progression in the liver, and a second line of chemotherapy (vinorelbine and capecitabine) was scheduled leading to an apparent stabilization. However, CA15.3, chromogranine A (CgA), neuron-specific enolase (NSE), and carcinoembryonic antigen (CEA) levels rose to 82 ng/ml (normal range < 34 ng/ml), 75 ng/ml (19–98 ng/ml), 20.6 ng/ml (< 18 ng/ml), and 32 ng/ml (< 4 ng/ml), respectively.

Table 1. Neuroendocrine tumor sites

Site	%
Digestive tract, total	64–68
Esophagus	0.6–1
Stomach	2–4
Small intestine	35–40
Colon/rectum	20–30
Appendix	7–8
Anus	0.1–0.5
Liver	0.32
Gallbladder	0.1–0–2
Pancreas	0.5–3
Digestive tract, NOS	2–3
Ovary	0.8–1
Testis	0.005
Other/thymus	0.2–0.3
Trachea/bronchi/lung	10–24

NOS = Not otherwise specified.

The lack of response to this second-line chemotherapy made it unlikely that a benefit be derived from other protocols, and therefore it was decided to focus on the striking NED. The overexpression of SSTR in the metastases was 'in vivo' detected by ^{111}In-pentetreotide scintigraphy. Both the scintigraphy and a whole body CT scan did not detect any additional locations. Tumor markers were as mentioned above (CA15.3 = 82 ng/ml, CgA = 75 ng/ml, NSE = 20.6 ng/ml, CEA = 32 ng/ml). Figure 1 depicts the liver CT scan prior to treatment. At that time, a phase II protocol to treat patients affected by gastroenteropancreatic neuroendocrine tumors (GEP-NETs) with the SSTR analog ^{90}Y-(DOTA)0-Tyr3-octreotide (^{90}Y-DOTATOC) was ongoing within our department. The institutional ethics committee permitted treatment of the BC patient following the same protocol as for GEP-NETs, and 2.57 GBq of ^{90}Y-DOTATOC were administered. No adverse reactions were recorded. Bremsstrahlung single photon emission CT carried out 4 days after ^{90}Y-DOTATOC therapy verified liver metastasis uptake (fig. 2).

Since the recruitment of this patient was unusual to our protocol, which is aimed to treat well-differentiated SSTR-positive GEP-NETs and not simply SSTR-positive cancers, we decided to obtain proof of efficacy of the therapy. For this purpose an abdominal CT scan was performed 1 month after the first treatment, which showed shrinkage of the metastasis located in the 6th liver segment (fig. 3) and a lowering of the vital components of the metastasis in the 3rd segment. A nearly 50% reduction in CA15.3 (from 82 to 47.2 ng/ml), CgA (from 75 to 44 ng/ml), and CEA (from 32 to 23.6 ng/ml) was recorded. The impressive response encouraged us to progress with the treatment for a further 3 bimonthly cycles, as was scheduled for the GEP-NETs trial. A CT scan 1 month after the 2nd cycle showed a further reduction in the lesions located in the 6th and 8th liver segment and the disappearance of another metastasis previously detected in the 3rd segment (fig. 4). Indeed, CA15.3 levels continued to decrease from 45 to 32 to 26.1 and eventually to 22 ng/ml. The same trend was noted for CEA and CgA. A CT scan carried out 1 month after the end of the complete line of PRRT showed persistence of 1 liver metastasis only, reduced in diameter from 33 to 13 mm (fig. 5). Biochemical marker levels measured at that time were CA15.3 20 ng/ml and normalized CEA and CgA. In order to gain the best therapeutic effect, it was proposed to the patient to reach the maximum tolerated dose (nearly 15 GBq) by adding 2 more cycles. However, she refused due to depression and self-reported claustrophobia. The patient was therefore

Table 2. WHO classification of neuroendocrine tumors with sensitivities of the principal tissue markers

Grade	Lung/thymus[a]	GEP-NET[b]	Sensitivity, %							
			CgA		CK fr		proGRP		NSE	
			lung	GEP	lung	GEP	lung	GEP	lung	GEP
Low	carcinoid	neuroendocrine neoplasia, grade 1	60	50	28	29	25	15	16	17
Intermediate	atypical carcinoid	neuroendocrine neoplasia, grade 2	73	63	46	38	59	75	36	63
		neuroendocrine carcinoma, grade 3 small-cell carcinoma								
	small-cell carcinoma	neuroendocrine carcinoma, grade 3 large-cell neuroendocrine carcinoma	33	54	59	70	76	54	48	54
High	large-cell neuroendocrine carcinoma	mixed neuroendocrine adenocarcinoma	59	67	65	36	53	17	53	75

[a]2000 classification.
[b]2010 classification.
GEP-NET = Gastroenteropancreatic neuroendocrine tumor.

scheduled for monthly follow-up with CA15.3, CEA, and CgA screening and a CT scan after 4 months.

Five months after the end of PRRT, CA15.3 and CEA levels began to rise, suggesting a biochemical relapse. This hypothesis was confirmed by 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT showing presence of metastasis and an enlarged hylar node. Thus, it was proposed to the patient to undergo a further 2 cycles of PRRT (January and March 2009) followed by 4 cycles of gemcitabine/oxaliplatin (GEMOX, May–July 2009). This achieved a transient stabilization of the disease. However, due to liver progression, further chemotherapy was attempted (capecitabine, metronomic cyclophosphamide, and methotrexate) from September 2009 to January 2010 without an objective response, and the patient died from liver failure in March 2010.

Discussion

Little is known about NED in BC, including its impact on prognosis and the possibility to take advantage of SSTR. SSTR overexpression in BC could make PRRT worthwhile, and to our knowledge this is the first report to describe a biochemical complete response together with shrinkage of the neoplastic masses after treatment with ^{90}Y-DOTATOC. Despite this being a report of a single case, we believe that certain suggestions may be derived from it. As already reported in the literature for other cancers [12–16], PRRT may be effective in neoplasms other than neuroendocrine tumors. Hopefully, and if confirmed in a large cohort of patients, this could determine an added value of PRRT in BC treatment. Moreover, in the era of treatments aimed at tumor stabilization, PRRT may provide objective and potentially striking tumor shrinkage even in aggressive disease. Finally, we suggest that PRRT may advance from being a second- or third-line therapy to a first- or second-line therapy within an intigrated schedule including all other therapeutic modalities for the treatment of both GEP-NETs and other SSTR-expressing neoplasms such as those described in this paper.

Disclosure Statement

None of the authors declare any competing interests within the last 3 years which might be perceived as influencing the results and/or discussion reported in this article.

Online Supplemental Figures

Fig. 1. Pre-therapeutic CT scan showing 1 of 3 liver lesions.
Fig. 2. Bremsstrahlung SPECT of the same metastases as in figure 1.
Fig. 3. CT scan at the same level as figure 1 after the first cycle of PRRT showing a reduction of the metastasis diameter
Fig. 4. Pre- (left) and post- (right) CT scan. Although the 2 slices are not exactly corresponding, it is possible to appreciate the disappearance of the 8th liver segment metastasis.
Fig. 5. CT scan after the 4th cycle of PRRT. The only metastasis detectable is reduced to 13 mm in diameter.

To access the online supplemental figures, please refer to *www.karger.com/DOI=000343612.*

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