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LETTER TO THE EDITOR

Successful treatment of high-grade pancreatic neuroendocrine neoplasms with everolimus

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Current systemic anti-tumor therapies for the treatment of neuroendocrine neoplasms (NEN) include somatostatin analogs (SSAs), cytotoxic chemotherapeutics, peptide receptor radionuclide therapy (PRRT) and molecular-targeted therapy. Following the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines, treatment choices are mainly based on tumor grade, primary tumor site and progression on treatment lines, requiring experience and knowledge in selecting the appropriate therapy [1]. Tumor grade is defined by the proliferation activity, determined as mitotic count or Ki67 protein staining. Tumors with Ki67 exceeding 20% are mostly poorly differentiated (G3) and are generally called neuroendocrine carcinomas (NEC) [2]. These high-grade malignancies are aggressive and usually require early onset of platinum-based chemotherapy [3]. However, more recently cases of NEC have been reported with more favorable disease course and Ki67 in the range of 20–50%. It is questioned if, within this patient population, platinum-based chemotherapy is required as first-line therapy. The mTOR inhibitor everolimus is a valid therapeutic option for low or intermediate grade (G1/G2) neuroendocrine tumors (NET), but data outside of regulatory trials are sparse and not available for high-grade neoplasms [4].

Acceleration of tumor grade by dedifferentiation have been described for several tumor types [5]. For NET however, very few cases have been published so far. Here, we describe two patients treated at an academic hospital in Germany, with advanced pancreatic NET who showed dedifferentiation from intermediate to high-grade. Due to general good condition and lack of further treatment options, both patients were treated with everolimus as last resource and showed radiological and clinical benefit.

Two patients were treated at an academic hospital in Germany. Despite several lines of systemic treatment, clinical and radiological progression was seen together with dedifferentiation of the tumor metastases, after six and five lines of prior therapy. Due to general good condition and lack of further treatment options, both patients were treated with everolimus as last resource.

Figure 1 summarizes the treatment over time in relation to the tumor burden for both patients. Measurements of the tumor and metastases were taken of radiological scans performed during the course of disease. Tumor burden was defined as the sum of the largest liver metastases, primary tumor and the largest pathological lymph nodes. Response to treatment was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [6].

The first patient, a 35-year-old Caucasian male, presented with a primary pancreatic tail mass, not suitable for resection, together with liver metastasis. Histopathology showed an intermediate grade NET (Ki67 5–10%) and palliative chemotherapy with fluorouracil (5-FU) and streptozocin was given for 12 months. The resulting partial remission made radical resection of the primary tumor possible, which revealed a proliferation rate of 2%. Over the course of the following 5 years, disease progression was treated with repeated regimen of streptozocin/5FU (6 months response), two times transarterial chemoembolization (TACE) (insufficient response), vatalanib (PTK787/ZK) within a clinical trial (progressive disease), 5FU/oxaliplatin (FOLFOX) (6 months response) and temozolomide/capecitabine (CAPTEM) (15 months response). In the presence of liver disease only, and lack of other established therapies, a partial liver resection was performed without any complications. Histopathology revealed an increase in Ki67 proliferation index to 25%, dedifferentiating the tumor to a NEC. A fifth-line systemic treatment with 5-FU, irinotecan and becavizumab was given to treat multifocal recurrence in the liver,

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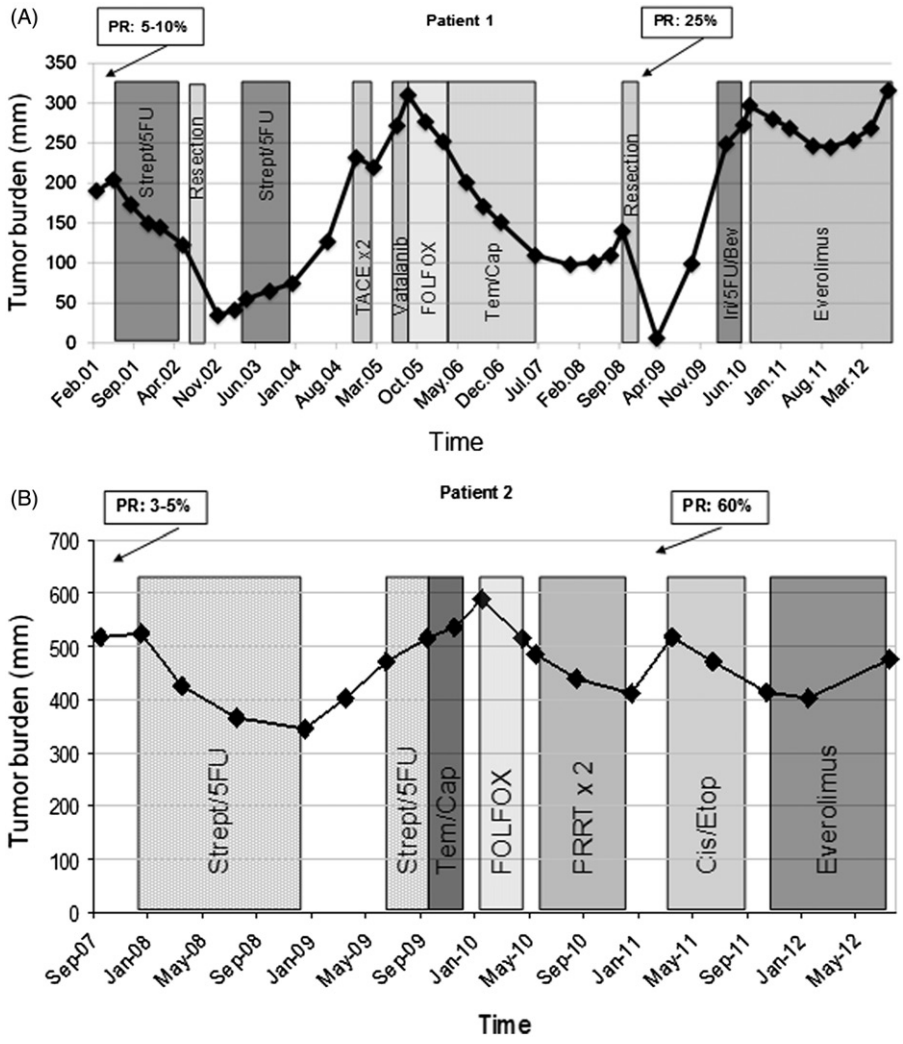

Figure 1. Tumor progression and regression shown in a curve over time between start of treatment and end of last treatment; A = case 1, B = case 2. Tumor burden is defined as the sum of the five largest liver metastases, primary tumor and 2 of the largest pathological lymph nodes. Measurements were taken of radiological scans performed during the course of the disease and treatments. Treatments given are represented by columns in grey. The widths of the column represents the treatment duration, with the exception for resection. PR: Proliferation rate; STZ/5FU: Streptozotocin/5-Fluorouracil; TACE x 2: Trans-arterial-chemoembolization performed two times; FOLFOX: Folinic acid-Fluorouracil-Oxaliplatin; Tem/Cap: Temozolomide/Capecitabine; Iri/5FU/Bev: Irinotecan/5-Fluorouracil/Bevacizumab; PRRT x2: Peptide Receptor Radionuclide Therapy performed two times; Cis/Eto: Cisplatin/Etoposide.

without response after three cycles. After a total of 112 months of alternating stable disease and five lines of systemic therapy, treatment with everolimus 10 mg daily was initiated. This was very well-tolerated and regular scans revealed durable response with stable disease for 2 years.

The second patient was a 44-year-old Caucasian man who presented with an unresectable pancreatic NET of 20 cm in size. Histopathology from biopsy showed a G2 NET with a Ki67 proliferation index of 3–5%. Palliative treatment with streptozosin and 5-FU resulted in partial remission for 12 months. Progressive disease lead to re-challenge of the same regimen followed by treatment with CAPTEM and FOLFOX, with unsatisfactory responses. Two cycles of PRRT resulted in a partial response, followed by rapid progression after 3 months with occurrence of new liver metastases and first occurrence of bone and intracerebral metastases. Resection of the solitary intracranial mass revealed a NEC with a Ki67 proliferation index of 60%. Subsequent treatment with cisplatin and etiposide was associated with remarkable objective response, but was terminated after 5 months because of peripheral neuropathy. As no other therapeutic options were available, a daily treatment of 10 mg everolimus was initiated. This was well-tolerated and resulted in minor tumor remission with revascularization of the portal vein after 3 months. In addition, FDG uptake of the primary tumor on PET-imaging decreased and the clinical condition of the patient improved remarkably. The response to everolimus lasted for 9 months, until progressive disease was seen again.

Successful treatment with everolimus in highly proliferating pancreatic NET is presented in two cases. In both patients, there was an increase of tumor grade during the course of the disease from intermediate to high-grade. Treatment options for pancreatic NET have improved over the last few years; however, were restricted to low and intermediate grade NET. Data on activity of targeted drugs in NEC G3 is still lacking. Following the ENETS Consensus Guidelines, treatment choices are mainly based on tumor grade, primary

tumor site and progression on treatment lines [1]. The use of targeted agents have been widely explored in Grade 1 and 2 NEN, although clinical trials frequently exclude NEC. Very few case reports have been published on the effect of everolimus for these high-grade tumors [7,8]. The induction of a long-lasting stable disease with everolimus in both patients, after years of alternating disease progression and multiple systemic treatments, is promising. Toxicity of everolimus is not interfering with the common dose limiting factor of neurotoxicity caused by platinum-based chemotherapy. This new treatment option needs further research, especially for platinum resistant carcinomas that show increase in proliferation from intermediate to high-grade, or possibly even in patients with primary high-grade NEC.

The heterogeneity of high-grade NEN is a recent topic of discussion. Some researchers propose a new classifications in which the group with the highest proliferation index will be divided into G3 neoplasms with favorable biological behavior (G3 NET) as opposed to G3 neoplasms with increased aggressive behavior (G3 NEC) [9,10]. The effect that is described in the presented patients might be explained by this difference in tumor behavior. More research on this topic is encouraged as this can have significant impact on the management of patients with high-grade NEN.

In summary, the diagnosis of high-grade NEC dedifferentiating from a previously classified lower grade NET might be a new disease entity with the potential use of the antitumoral effect of everolimus that has been presented in lower grade NET, as shown in these cases. Further confirmation in prospective clinical trials is warranted.

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LETTER TO THE EDITOR

Unilateral hippocampal wasting after combined-modality therapy for glioblastoma

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