Capecitabine plus temozolomide in well- or moderately--differentiated primary atypical neuroendocrine tumours — single-centre experience of two cases

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Abstract

Introduction: Neuroendocrine neoplasms (NENs) are a rare and heterogeneous group of tumours, with a variety of primary origins and variable aggressiveness. NENs with an atypical primary origin, such as breast and retroperitoneal NENs, are extremely rare. As a consequence, an established diagnostic and therapeutic strategy in this particular subgroup is lacking. The combination of capecitabine and temozolomide, called CAPTEM regimen, has produced promising response rates in patients with grade 1 or 2 neuroendocrine tumours of multiple origins.

Case presentation: The first is a case of a 68-year-old woman with a metastatic primary breast neuroendocrine tumour, treated with cisplatin plus etoposide as first line, followed by CAV scheme (cyclophosphamide, doxorubicin, and vincristine), and subsequently treated, in third line with the CAPTEM regimen, obtaining radiological response and good tolerance. The second is the case of a 66-year-old woman affected by a metastatic primitive retroperitoneal NET G2. The patient progressed after a somatostatin analogue-based first line, whereas the CAPTEM regimen led to a partial and durable response with a favourable safety profile.

Conclusions: CAPTEM chemotherapy has been shown to be an active and safe therapeutic option in advanced, metastatic G1/2 atypical primary NENs. **(Endokrynol Pol 2019; 70 (4): 380–383)**

Key words: capecitabine; temozolomide; atypical primary; neuroendocrine tumours; efficacy; safety

Introduction

Neuroendocrine neoplasms (NENs) are a rare and heterogeneous group of tumours, with a variety of primary origins and variable aggressiveness [1]. However, in clinical daily practice, therapeutic management is determined by the combined evaluation of the tumoural morphology, the proliferation index (Ki67) value, and the clinical presentation (tumour burden, rapidity of growth, patient's performance status), whatever the primary origin. Of note, clinical trials and the most relevant retrospective studies generally do not include patients with NENs of atypical origin, thus a standardised therapeutic strategy has not been established in this particular subgroup. As a consequence, in clinical practice, well- and moderately-differentiated NENs (defined as neuroendocrine tumours with grading 1/2 or NENs G1/2) with atypical primary sites of origin, such as primary breast [2] and primary retroperitoneal NETs [3], are treated like more common primary ones – gastroenteropancreatic and thoracic NENs. However, increasing literature data suggest that the combination chemotherapy of capecitabine and temozolomide (CAPTEM) could be a potentially useful treatment option for patients with grade 1/2 NENs of multiple origins [4–10]. Here we describe two cases of G1/2 NENs with atypical primary treated with CAPTEM regimen.

Case reports

Case 1

A 68-year-old woman, suffering from neuroendocrine primary breast cancer, with bone, lymph node, lung, brain, liver, and left adrenal metastases is described herein. Following the auto-detection of a left breast node, in June 2010 the patient performed an ultrasound with evidence of two suspicious lesions in the left breast. In September 2010 the patient underwent a left breast lumpectomy with sentinel lymph node dissection. At histopathologic examination, the infiltrating tumour revealed features of moderately differentiated, G2, pT1bN1 neuroendocrine tumour, with a multifocal component. The left axillary sentinel lymph node showed metastatic deposits with the same histomorphology.

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Immunohistochemistry (IHC) studies with antibodies directed against chromogranin, synaptophysin, oestrogen receptor (ER), progesterone receptor (PgR), and HER2/neu, were carried out. More than 90% of tumour cells, in both breast and lymph nodes, were positive for chromogranin and synaptophysin, whereas ER, PgR, and HER2 were negative. Ki-67 was 16%; somatostatin receptor results were negative. Thus, in October 2010, the patient underwent an axillary left dissection. At the histologic assessment, reactive hyperplasia was detected in all 11 examined lymph nodes. Both basal serum chromogranin A and NSE were within normal ranges. The patient did not show clinical signs of carcinoid syndrome. A postoperative total body (TB) computed tomography (CT) scan was performed, with the evidence of bilateral mediastinal pathological lymph nodes, liver, lung, left adrenal metastases, three secondary brain lesions, and bone lytic secondary lesions in the spine and ribs. The result of the bone scan and In-111 Octreoscan scintigraphy was negative. From November 2010 to March 2011 the patient received the combination of cisplatin and etoposide as first-line chemotherapy, considering the high tumour burden and the patient's good clinical condition. The patient developed grade 3 haematological toxicity and fatigue; therefore, a dose reduction was needed. After six cycles of treatment, the restaging CT scan showed a partial response of bone, lymph node, hepatic, adrenal, and lung lesions, whereas brain lesions were stable. Therefore, the patient underwent pan-encephalic palliative radiotherapy, with a total dose of 30 Gy. From July 2011 to May 2013, a "wait and see" strategy was carried out, and bisphosphonates therapy (zoledronic acid) was added for 24 months. Due to disease liver progression, from June to November 2013, the patient received eight cycles of CAV chemotherapy (cyclophosphamide, doxorubicin, and vincristine) with the onset of G3 neurotoxicity. In November 2013, the restaging TB CT scan showed a partial response. A "wait and see strategy" was chosen again. On March 2015 after a new radiological progression, a fine needle biopsy was performed. The histopathological evaluation detected neuroendocrine differentiation cells with a Ki-67 of 2%; the IHC ER, PgR, and ERB-B2 were negative. In April 2015, a third-line chemotherapy with oral capecitabine (2000 mg/m² daily, days 1–14) and temozolomide (200 mg/m² once daily, days 10–14) every 28 days (CAPTEM scheme) was started. After six cycles, the patient obtained a radiological reduction of brain lesions and the stability of the other metastatic lesions. The patient experienced grade 3 thrombocytopaenia after four cycles of therapy, so a 25% dose reduction was performed for a further two cycles, followed by a 50% dose reduction for a further two cycles. In January 2016, a TB CT scan showed stable

disease, but progressive severe cognitive deterioration led to cessation of active anticancer treatment. After six months the patient died.

Case 2

In 2011, a 66-year-old woman performed an abdominal CT scan for persistent abdominal pain, with evidence of retroperitoneal neoplastic lesion. The woman had a remote pathological history of autoimmune hypothyroidism that was well controlled by replacement therapy, parathyroid adenoma excision, and type 2 diabetes requiring oral hypoglycaemic treatment. The patient underwent a radical surgical removal of the disease. Histopathologic examination showed a moderately differentiated neuroendocrine tumour (NET); Ki-67 value amounted to 4% (NET G2); necrosis and angioinvasion were absent. The screening for inherited endocrine syndromes was negative. Post-surgery Gallium 68 PET-CT scan was negative. No adjuvant therapy was performed, and clinical-radiological follow-up was set. Three years after diagnosis, a CT scan showed liver disease progression, confirmed by biopsy. At the clinical evaluation, the patient presented carcinoid syndrome, reporting frequent episodes of flushing and diarrhoea. A first-line therapy with the intramuscular somatostatin analogue Octreotide LAR 30 mg every 28 days was started, with a significant improvement of the carcinoid syndrome symptoms. A worsening of diabetes was observed, with the need for insulin therapy. After about one year of therapy, in November 2015, a total body CT scan showed further hepatic disease progression. The case was discussed within the neuroendocrine multidisciplinary board of our centre, and a second-line CAPTEM chemotherapy was proposed. After the first cycle of chemotherapy, the patient experienced grade 3 thrombocytopaenia, and a dose reduction was performed for a further eight cycles. In July 2016, after hepatic oligo-progression of the disease, the case was discussed again in the neuroendocrine-dedicated multidisciplinary team, and a hepatic trans-arterial chemoembolism with epirubicin was performed, obtaining a partial response. In June 2018, at 20 months of follow-up, the patient was in good clinical conditions, without carcinoid syndrome or disease progression, receiving octreotide LAR treatment.

Discussion

A variety of therapeutic strategies, such as somatostatin analogues, molecular therapies, peptide receptor radionuclide therapy (PRRT), and chemotherapy regimens, have been investigated and approved in inoperable or metastatic G1/G2 NET patients [11]. However, standard cytotoxic agents commonly used in clinical practice

have demonstrated limited efficacy [12]. The association of temozolomide, an orally administered alkylating agent that methylates the O6-residues of guanine, thus preventing DNA duplication during cell proliferation and inducing cell death, and capecitabine, the orally administered precursor of 5-fluorouracil (5-FU), have demonstrated activity in the treatment of G1/G2 NET of pancreatic and non-pancreatic origin with a favourable toxicity profile [6, 10]. Recently, the most common mechanism of resistance to temozolomide, consisting of high expression of O⁶-methylguanine DNA methyltransferase (MGMT), a DNA repair enzyme able to reverse the anti-tumour effect of this alkylating drug, has been identified [13]. *In vitro* studies showed that 5-FU depletes tumour levels of MGMT [14], and this represents a strong rationale to test the synergistic activity of capecitabine and temozolomide.

Recently a randomised phase II trial compared capecitabine alone and the CAPTEM regimen in metastatic pancreatic NET. Temozolomide and capecitabine improved the progression-free survival (PFS) of 8.3 months (HR 0.58) compared to temozolomide alone. This was the first prospective randomised trial of these agents and showed the longest PFS reported for pancreatic NET-directed therapy [15].

To the best of our knowledge, as of June 2018, there are five ongoing studies, all recruiting patients, designed to explore the role of CAPTEM association in NENs (Tab. I), but none of these studies is specifically designed for unknown primary NET (NCT03387592, NCT03279601, NCT03079440, NCT02595424, NCT02358356).

This work presented two cases of atypical primary NET: the first was a primitive breast NET and the second was a primary NET of the retroperitoneum, both treated with CAPTEM. Primary neuroendocrine breast tumour was defined as a separate subtype of breast cancer in 2003 by the World Health Organisation (WHO). This rare malignancy has an incidence of 0.3 to 1% of all breast cancers [16], occurring predominately in postmenopausal women [17]. The histopathological assessment of these tumours is difficult, and in most cases the correct diagnosis is made after proper examination of the postsurgical specimen [18].

In our experience CAPTEM determined a partial response in a heavily pre-treated neuroendocrine breast tumour. Also, the combination showed activity in reducing brain metastases. As is known, the TMZ significantly improves the survival of patients with newly diagnosed glioblastoma due to its relative penetration across the normal blood–brain barrier [19].

Primary NENs of the retroperitoneum are extremely rare, being more commonly the site of metastases from NETs with known primary. Only a few cases are reported in the literature [3].

As a consequence, the identification and treatment of these atypical NETs represent a clinical challenge and an essential need to identify the best treatment options. In clinical practice, therapeutic strategies for NENs of atypical primary are not well established,

Table I. *Ongoing studies exploring the efficacy and safety of the association of capecitabine and temozolomide in neuroendocrine tumours*

Clinical trials gov identifier	Title	Conditions	Interventions
NCT03387592	CAPTEM or FOLFIRI as second-line therapy in neuroendocrine carcinomas	Neuroendocrine carcinoma	CPT-11/Calcio levofolinate/5-fluorouracil
			Capecitabine/temozolomide
NCT03279601	Study to compare capecitabine combined with dacarbazine (CAPDTIC) versus capecitabine combined temozolomide (CAPTEM) in advanced and metastatic gastrointestinal pancreatic and oesophageal neuroendocrine tumour	Gastrointestinal, pancreatic, or oesophageal neuroendocrine tumour	Capecitabine/dacarbazine
			Capecitabine/temozolomide
NCT03079440	TEMCAP in grade 3 and low Ki-67 gastroenteropancreatic neuroendocrine tumours	Gastrointestinal or pancreatic neuroendocrine carcinoma	Capecitabine/temozolomide
NCT02595424	Cisplatin, carboplatin, and etoposide or temozolomide and capecitabine in treating patients with Neuroendocrine carcinoma of the gastrointestinal tract or pancreas that is metastatic or cannot be removed by surgery	Gastrointestinal or pancreatic neuroendocrine carcinoma	Capecitabine/temozolomide
			Carboplatin or cisplatin/etoposide
NCT02358356	Capecitabine ONTemozolomide radionuclide therapy octreotate lutetium-177 neuroendocrine tumours study (CONTROL NETS)	Intestinal or pancreatic neuroendocrine tumour	Lutetium-177 octreotate (¹⁷⁷Lu-octreotate) peptide receptor radionuclide therapy (PRRT) plus capecitabine/temozolomide
			Capecitabine/temozolomide

so the CAPTEM regimen, which is active and well tolerated, can be considered for the treatment of these particular tumours after the failure of a first-line treatment.

Conclusions

Given the prior reports of the capecitabine and temozolomide combination in G1/2 NETs, as well as our two cases, use of the CAPTEM regimen should be considered in patients with advanced, metastatic, well- or moderately-differentiated neuroendocrine tumours, including those of atypical primary, such as retroperitoneal or breast origin that fail conventional medical and surgical therapies. Additional larger scale studies are needed to define the role of this chemotherapy regimen in the treatment of aggressive tumours.

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CASE REPORT