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Systemic therapies in metastatic pancreatic neuroendocrine neoplasms (PNENs): is there a right sequence? A case report and review of the literature

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Summary. Management of pancreatic neuroendocrine neoplasms (PNENs) is very complex and heterogeneous; the right therapeutic strategy closely depends on a multidisciplinary approach. We report the case of a 35-years-old man with an advanced pancreatic neuroendocrine tumour (PNET). Initially individual specialists handled the case. After disease progression the clinical strategy was managed within a multidisciplinary team framework and the patient received various therapies thanks to integration of team expertise. He died 7 years after the first diagnosis.

Key words: PNENs, everolimus, temozolomide, chemotherapy

«Terapie sistemiche nelle neoplasie neuroendocrine pancreatiche (PNENs): esiste una sequenza corretta? Caso clinico e revisione della letteratura»

Riassunto. La gestione delle neoplasie neuroendocrine del pancreas (PNENs) è molto complicata ed eterogenea; per questa ragione, la definizione di una corretta strategia terapeutica dipende strettamente da un approccio multidisciplinare. Descriviamo il caso di un uomo di 35 anni con tumore neuroendocrino del pancreas (PNET) avanzato. Inizialmente la storia clinica del paziente è stata gestita da singoli specialisti che hanno pianificato singoli trattamenti. A seguito della progressione di malattia, il caso è stato gestito nell'ambito di un gruppo multidisciplinare ed il paziente ha potuto beneficiare di molte terapie grazie all'integrazione delle competenze e dell'*expertise* dei vari membri del gruppo. Il paziente è morto dopo circa 7 anni dalla diagnosi.

Parole chiave: neoplasie-neuroendocrine-pancreatiche, everolimus, temozolomide, chemioterapia

Introduction

The incidence and prevalence of pancreatic neuroendocrine neoplasms (PNENs) have increased over the last few years (1). According to the 2010 WHO classification, PNENs are classified as G1 (Ki67 ≤2%), G2 (Ki67 3-20%), referred to as neuroendocrine tumours (PNETs), and G3 (Ki67>20%) carcinomas (PNECs) (2). Depending on the association with syndromes related to hormone secretion, they may be functioning or non-functioning. Most patients with PNENs are metastatic at diagnosis, and outcome in this population is still unsatisfactory (a survival rate of 15% at 5-years) (3).

Somatostatin analogs (SSAs) are the mainstay in managing functioning NETs, because of their role

in symptom control and their antiproliferative activity suggested by both retrospective and prospective results (4, 5). Similarly, interferon alfa-2b (IFN) can help with symptomatic patients and can induce stabilization of progressive disease (6). Encouraging results have also been reported with peptide receptor radiotherapy (PRRT) although no prospective phase III studies have yet been published (7, 8). While platinum-based chemotherapy is a well-recognised approach in PNECs, no chemotherapy standards for NETs are nowadays available. Before 2011, streptozotocin (STZ) was the only approved agent for unresectable disease either alone or in combination with doxorubicin or 5-fluorouracil (5-FU) (9). Everolimus (EVE) and sunitinib (SUN) activity in PNETs has also been recently investigated, leading to approval of both tyrosine-kinase inhibitors (TKI) by the FDA, EMA and AIFA (10, 11). Moreover, recently Lanreotide has proved efficacious in grade 2 (<10% Ki67, CLARINET study) (12) non functioning enteropancreatic NENs, as well as in a well-conducted phase 3 randomized controlled trial (RCT).

Several factors need to be taken into account in defining the best treatment strategy in PNETs, including the treatment goal, patient and tumour features, data from the literature and guidelines, legislation and logistics. Given the multiple choices available, and the absence of specific data in the literature, the treatment sequence still remains a challenge to medical oncologists, and several questions on the best strategy are still unanswered.

Case report

A 35-year-old male patient with no previous medical history presented in April 2006 with uncontrolled vomiting and abdominal pain. He underwent an abdominal computed-tomography (CT) showing the presence of a pancreatic mass associated with abdominal lymphadenopathy and multiple liver lesions. Histology from a transcutaneous liver biopsy revealed a moderately differentiated PNET according to the 2000 WHO classification (13). Staining for synaptophysin was positive, negative for chromogranin-A (CgA), and the proliferation index (Ki67) was 3-4%. The level of plasmatic CgA was almost three times above the normal limit. A total body ^{111}Indium-Octreotide scintigraphy (SRS) was performed, showing a high somatostatin receptor (SSTRs) uptake in the liver, pancreas and abdominal nodes. Due to the extent of the disease, surgery was ruled out and PRRT (^{90}Yttrium-DOTATOC) was administered between June 2006 and October 2007 (total dose of 300 mCi). The patient was started on a follow-up programme lasting until March 2008 when a thorax-abdomen-pelvis (TAP) CT scan showed a progression of the pancreatic mass according to RECIST 1.0 criteria, and stability of the known lymphonodal and liver lesions. A^{68}Gallium-PET-CT highlighted the occurrence of multiple bone metastases. He then came to our attention and, between April and July 2008 received metronomic capecitabine (CAP; 2000 mg per day p.o. continuously), bevacizumab (BEV; 5 mg/kg i.v. biweekly), and octreotide (OCT; 30 mg s.c. every 28 days) long acting repeatable (LAR) in a phase II clinical trial (XELBEVOCT) (14); zoledronic acid (ZA; 4 mg i.v. every 28 days) was also started. A new TAP CT showed a partial response (PR) and a reduction of the CgA plasmatic level greater than 50% was observed. Due to the relatively long time between diagnosis and disease progression, a second transcutaneous liver biopsy was performed to verify the previous histological features (grading and Ki67) and assess the mTOR status The diagnosis of moderately differentiated PNET was confirmed (2000 WHO classification), Ki67 was 4%, and immunohistochemistry (IHC) revealed mTOR phosphorylation. In September 2009 the patient was asymptomatic and his performance status according to the ECOG scale was 0; due to progressive disease (PD) in the liver and an increasing plasmatic level of CgA, the patient was started on EVE (10 mg o.d.), obtained as off-label use. Octreotide was continued beyond progression. Treatment was well tolerated (grade 1 anaemia) and continued until January 2010, when it was discontinued due to liver PD and increasing plasmatic CgA (15). Thus, in March 2010, temozolomide (TMZ) 300 mg total dose per day over 5 days every four weeks was started, and OCT LAR/ZA was continued. PR was observed by a TAP CT scan and over 50% CgA blood level decrease. Temozolomide was well tolerated except for grade 1 nausea and hand-foot

dysesthesia and the patient felt well during this treatment (15). After 6 months, TMZ was discontinued and SUN started, ("off-label") due to PD in the liver. The patient was given 37.5 mg per day, 4 weeks on/two weeks off; subsequently, this was switched to 37.5 mg continuous daily dose because of good tolerance and an increasing level of plasmatic CgA, achieving disease stabilization as the best response. In September 2011 the patient complained of mild fatigue and his ECOG performance status was 1; because of further liver and lymphnodal PD, he received chemotherapy with CAP (2000 mg/m² per day over 14 days) and oxaliplatin (130 mg/m² i.v.) every 3 weeks (CAPOX). Grade 1 nausea and grade 2 peripheral neuropathy were the main toxicities recorded (15). Disease stability was achieved after 6 cycles of CAPOX; oxaliplatin was subsequently stopped and CAP continued until May 2013, when the patient developed pulmonary and liver progression. A new liver biopsy in February 2013 showed the same biological features (grade of differentiation, Ki67 and mTOR phosphorylation). From June to August 2013, TMZ was added to CAP and then, due to worsening of performance status (ECOG performance status 3) and further clinical progression, only supportive care was offered. The patient died in November 2013.

Discussion

Despite the increasing number of therapeutic options for patients with PNET, the evidence of improved performance by some of them over the last decades and the availability of multiple guidelines published by the major societies engaged with this disease, a clear algorithm on the most appropriate strategy is still lacking and the sequence of treatments seems to be mostly arbitrary. There is a general consensus that patients with NETs should be managed in a multidisciplinary team at reference centres, with data in the literature suggesting that this might be associated with an improvement in survival (16, 17). In the present case report, the patient was initially managed in a mono-disciplinary basis, obtaining isolated opinions from individual specialists on single treatment approaches (e.g. surgery, PRRT). Subsequently, he was enlisted in a multidisciplinary team, which allowed a more personalized treatment strategy, and probably accounted for the favourable survival reported (nearly 7 years). The choice of PRRT as a first-line treatment stemmed from multiple reasons: a high SSTR uptake, the patient's difficulty in accepting unresectability and the need for a chronic medical therapy, the absence of any widespread awareness of the role of chemotherapy for low-grade tumours among Italian oncologists or any well-established tradition of PRRT. However, the role of PRRT as a first-line treatment is still controversial, and its value in this case could be debated, given the tumour stability at baseline and the absence of any previous attempt with SSA single-agent therapy. The overall response rate (ORR) for PRRT has been reported in the range of 30-40%, with some heterogeneity due to different populations, study designs, schedules, and doses. High SSTR uptake and a limited number of small-size liver metastases have been found to predict response (Krenning score) (18-21). Renal and bone marrow toxicity have been reported, but rarely and often late.

One crucial point is the importance of a complete initial work-up: the patient came to our attention with progressive bone disease, highlighted by ^{68}Gallium-PET-CT-DOTA, which is more accurate for disease evaluation than SRS (22). Because of the different image modalities (SRS baseline, Gallium PET as reassessment) there was a risk of overestimation, which might have affected the subsequent therapeutic decision. We approached the patient's case through a multidisciplinary discussion, taking into consideration the various factors previously mentioned, and trying to design the whole sequence of treatment instead of identifying the next step only. In 2006 SUN was not available for non-functioning intermediate-grade advanced PNETs, while EVE was only allowed within clinical trials, SSA and IFN were registered by Italian authorities and studies with ^{90}Y-PRRT were ongoing (23). NETs are highly vascularized tumours, potentially responsive to VEGF inhibitors and sensitive to the antiangiogenic activity of protracted, continuous, low-dose chemotherapy schedules (metronomic chemotherapy). This was initially suggested by a phase II study, combining LAR OCT with continuous 5-fluorouracil infusion in previously untreated well-differentiated NET patients

(24). The results showed 93% disease control rate with a median of 22.6 months (range 2.7-68.5) time-to-tumor progression (TTP) . Minimal toxicity was observed. A second study, evaluating the combination of a metronomic oral TMZ schedule, bevacizumab and OCT in 15 patients with advanced NETs progressing on previous therapy, showed encouraging results (median 36 weeks TTP; 64% overall response rate). All grade toxicity was observed in 40% of patients, with only one patient being graded G3 (25). On these bases, we believed that inclusion in the XELBEVOCT trial could be a valuable option, achieving SD as best response and a good toxicity profile.

When the disease progressed further, enrolment in the RADIANT-3 study having concluded, the patient was started on EVE in off-label mode; however the RADIANT-3 trial, a phase III study that led to approval of everolimus in PNET, did not provide any data as to EVE activity after PRRT and, until today, there is still an unmet need for reliable predictive factors improving identification of patients who might benefit from this drug. For instance, an IHC analysis performed lately on the patient's specimen revealed a high p-mTOR expression, which was, however, associated with a short TTP (4 months) (26).

TMZ monotherapy was administered when the disease continued to progress on EVE therapy, as allowed by an extension of Italian "Law 648" (27). Although TMZ administration in PNET is still debated, there is increasing evidence of its potential activity, with ORR reported as being in the range of 8-70%. This extreme variability can be justified by the different administration modalities (alone or in combination, different schedules), different tumour features and the different methylation status of the DNA repair enzyme O6-methylguanine-DNA-methyl-transferase (MGMT), which has been shown to correlate with response (28-31). MGMT methylation was encountered in our patient, consistently with the prolonged disease control observed (6 months) (Fig. 1A, 1B, 2A, 2B).

Given the impossibility of being enrolled in the SUNITINIB phase III study, when further progression occurred the patient was started on SUN used off-label, which brought stability for approximately 12 months. Although the efficacy of everolimus-sunitinib (and vice versa) is debated as a sequence, there is preclinical evidence suggesting that resistance to VEGFR-targeted therapies could be mediated by tumour and environmental changes through activation of growth factor signalling including FGF/FGFR, HGF/MET, G-coupled protein receptors, and TGF-beta receptor (32, 33). Since mTOR transduces its signal downstream for many of these receptors, there might be a rationale for using EVE at a time of progression on SUN (34).

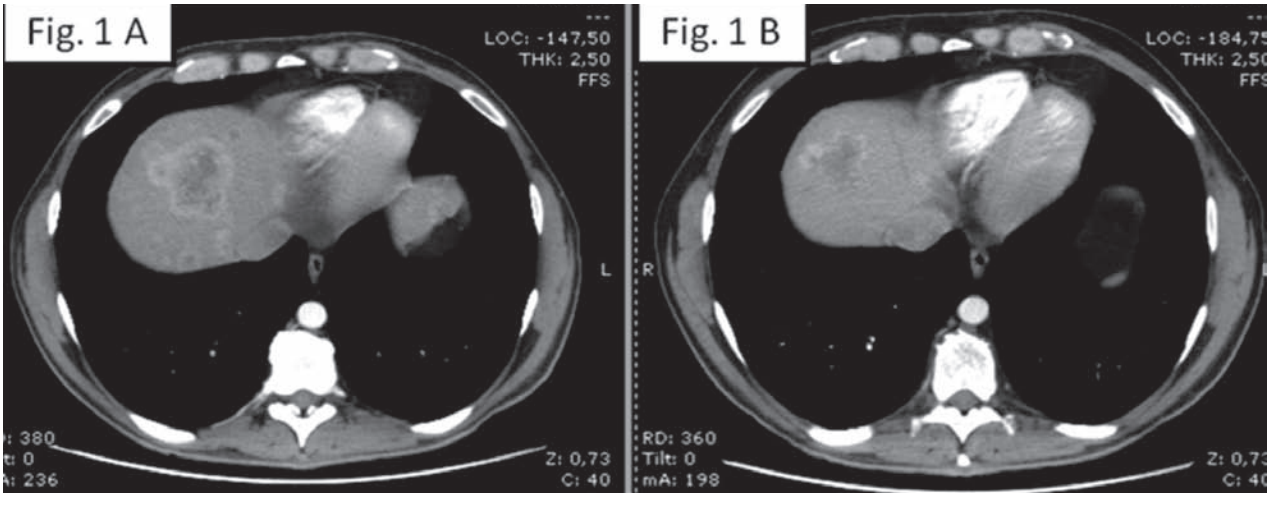

Figure 1. Abdominal CT scan in arterial phase before (A) and after (B) treatment with temozolomide showing partial response (PR) of liver lesions.

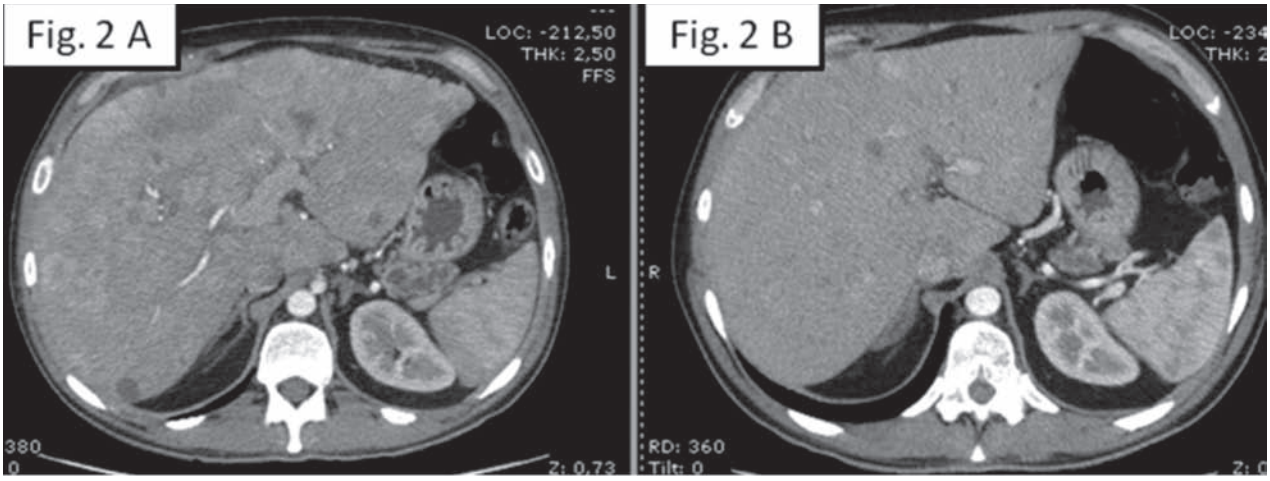

Figure 2. Abdominal CT scan in arterial phase before (A) and after (B) treatment with temozolomide showing partial response (PR) of liver lesions.

After bilobar hepatic progression, chemotherapy was re-introduced. A combination of oxaliplatin and capecitabine (CAPOX) or gemcitabine (GEMOX) has shown favourable results in advanced NETs, with ORR in the range of 63-84% and some advantage in survival (35, 36). Ongoing studies in advanced pretreated NET patients are currently evaluating the combination of oxaliplatin-based regimens and bevacizumab, reporting an ORR above 70% (37, 38). In our patient, CAPOX was administered for 6 cycles, resulting in SD. The thymidylate synthase (TS) status was also explored through pyrosequencing, leading to detection of 2R/3R polymorphism, which is known to correlate with positive clinical outcome in patients receiving fluoropyrimidines. After 6 cycles of CAPOX, oxaliplatin was discontinued because of cumulative toxicity and metronomic CAP was continued until further PD. CAP is an oral prodrug of 5-FU, offering an attractive alternative to prolonged intravenous infusions (24). Capecitabine has been tested in NETs, both as a monotherapy and in combination with oxaliplatin (39, 40).

Conclusion

Despite the multiple treatment options developed for patients with NETs over the last few years, representing an important step forward, the best therapeutic strategy for these patients is still controversial, generating confusion and inconsistency among physicians. Several clinical, pathological and regulatory factors need to be taken into account in the design of a best sequence, and discussion within a multidisciplinary team is nowadays highly encouraged. Since molecular targeted agents today play a crucial role in the management of these patients, it has become urgent to validate more appropriate criteria for response, RECIST currently being anachronistic.

For instance, based on our clinical practice, in patients with a non-functioning, asymptomatic, well-differentiated PNET with a low tumour burden starting with somatostatin analog could be a reasonable first-line choice, because of the good safety profile of this drug. In patients progressing on somatostatin analog, molecular targeted therapies such as Everolimus and Sunitinib could be used, taking into account the regulatory approval and different safety profile of these drugs, as well as the tumour characteristics and patient comorbidities. On further disease progression, temozolomide-based chemotherapy or PRRT might be the logical next choices; they could in some cases be used earlier in the sequence of treatment, particularly in highly symptomatic patients and when the main goal of treatment is to achieve tumour shrinkage rather than disease stabilization. Somatostatin analogs, which are the mainstay of treatment of patients with functioning PNET, can be also combined with other treatments such as targeted therapies or chemotherapy.

To conclude, given the long life-expectancy in patients with low grade NENs, when it comes to defining the right therapeutic strategy extreme attention should be paid to the patient's quality of life and potential treatment-related late toxicities.

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