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Oxaliplatin-based second-line chemotherapy in neuroendocrine carcinomas. A case series and review of the literature

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Summary. Patients with metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) are generally treated with a first-line chemotherapy including cisplatin and etoposide, in the absence of randomized trials. No specific second-line regimen has been reported. According to some retrospective data, platinum rechallenge could be considered in GEP-NECs. However, in view of the considerable platinoid toxicity profile, it would be advisable to consider an analogue thereof in order to minimize cumulative toxicity. We present the clinical history of three metastatic GEP-NEC patients who underwent oxaliplatin-based second-line chemotherapy after progression on platinum-based first-line chemotherapy.

Key words: gastroenteropancreatic; neuroendocrine carcinomas; oxaliplatin; second-line chemotherapy

«Chemioterapia di seconda linea a base di oxaliplatino nei carcinomi neuroendocrini. Una serie di casi clinici e revisione della letteratura»

Riassunto. I pazienti affetti da carcinoma neuroendocrino gastro-entero-pancreatico (GEP-NECs) sono abitualmente trattati con chemioterapia di prima linea a base di cisplatino ed etoposide, in assenza di studi randomizzati. Uno specifico regime di seconda linea non è stato riportato. In accordo con alcuni dati retrospettivi, il ritrattamento dei tumori GEP-NEC con un platino potrebbe essere considerato. Comunque, alla luce del considerevole profilo di tossicità dei platinoidi, sarebbe indicato considerarne un analogo in modo da minimizzare la tossicità cumulativa. Presentiamo la storia clinica di tre pazienti affetti da GEP-NEC metastatico sottoposti a terapia di seconda linea a base di oxaliplatino dopo essere progrediti a una prima linea di chemioterapia platino-basata.

Parole chiave: gastroenteropancreatici; carcinomi neuroendocrini; oxaliplatino; chemioterapia di seconda linea

Background

Gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) are very rare and aggressive, accounting for 5-10% of GEP neuroendocrine neoplasms (NENs) (1).

In a large Italian database, which included 820 patients with various types of neuroendocrine tumors (NETs), 63% were GEP-NENs and 7% of them were GEP-NECs (2). According to the WHO 2010 classification, neuroendocrine carcinomas are characterized by a high mitotic count (more than 20/10 HPF) and/

or Ki-67 proliferation index >20% (3). Gastroenteropancreatic NECs may arise in different regions of the gastro-intestinal tract: esophagus, stomach, pancreas, ileum and colon. Based on their behavior and features, GEP-NECs are assimilated to small cell lung cancer (SCLC). In the metastatic setting, the use of a platinum-based chemotherapy has been recommended since 1991 (4). The combination of cisplatin (CDDP) or carboplatin (CBDCA) and etoposide (E) is widely applied as first-line treatment while a second-line chemotherapy has yet to be established.

Oxaliplatin, L-OHP, is a third generation platinum analogue in which the 1,2-diaminocyclohexane (DACH) ligand substitutes for the amino groups of cisplatin. The antitumor activity of oxaliplatin, inhibiting DNA synthesis, is based on the formation of DNA adducts which are more bulky and more hydrophobic than those formed by cisplatin (5).

The use of oxaliplatin in combination with other drugs is well-established in the treatment of the main GEP adenocarcinomas.

In solid tumors the probability of response to second-line treatment normally depends on the best response to previous therapy. Rechallenge of the same or an analogous drug after a drug holiday, following disease relapse or progression, is more commonly used today; for example, cabazitaxel, a novel tubulin-binding taxane, is effective in patients with adenocarcinoma of the prostate previously treated with docetaxel (6) and the reintroduction of a platinum-based chemotherapy is a well-established practice in advanced ovarian cancer (7).

In this mini-review and case series, we discuss the use of an oxaliplatin-based chemotherapy in metastatic GEP-NECs on or after progression to a platinum-based first-line therapy.

Case 1

In December 2010, a 74 year-old Caucasian man underwent a full-body contrast medium computed tomography (CT) scan showing a mass of pancreatic head, adherent to the common hepatic artery and encasing celiac vessels, and multiple lung micro-nodules. The patient underwent debulking surgery of the primary tumor with histological diagnosis of a poorly differentiated pancreatic NEC with a ki-67 index of 42%.

From January to March 2011, he was treated with CBDCA/E every 21 days for 3 cycles with radiologic partial response (PR) and two further cycles were administered with maintenance of response. Then, due to a herpes zoster infection the treatment was discontinued.

In September 2011, after an interval of more than 4 months from the last cycle of CBDCA/E, progression disease (PD), consisting in increased pancreatic lesions and appearance of a small nodule in the right pectoral muscle, was observed. The chemotherapy was resumed and stable disease (SD) was documented after 3 cycles. On that basis, CBDCA/E was kept on up to a total of six cycles until February 2012, and then stopped due to progression of the pectoral metastases (whereas primary tumor and lung nodules were stable). No further chemotherapy was performed by physician's decision.

Five months later from the last cycle of CBDCA/E, because of further PD at CT scan, a subsequent chemotherapy with oxaliplatin and capecitabine (XELOX regimen) was started. After the first 3 cycles the pectoral nodule disappeared and the other lesions were stable (September 2012). After 6 cycles, the disease was globally stable so the therapy was continued until the 8th cycle. Due to further PD about 1 year after the last cycle of XELOX, the patient died in February 2014.

Case 2

A 64 year-old Caucasian woman, was admitted to the emergency room due to abdominal pain in May 2009, with a diagnosis of bowel obstruction. A barium enema showed tight stenosis of the transverse colon and a full-body CT scan showed wall thickening in the transverse colon, presence of some mesenteric lymphadenopathies and multiple liver metastases (maximum diameter of 5 cm). A somatostatin receptor scintigraphy (SRS) was negative. The patient underwent palliative transverse and left hemicolectomy and locoregional lymphadenectomy. Histological examination reported G3 NEC of large bowel invading serosa,

Ki-67 55%, vessel and lymphatic infiltration, with 1 out of 5 lymph-nodes positive and resection margins negative.

In June 2009 the patient came to our attention, and we proposed a first-line chemotherapy with CBDCA/E. After 6 cycles a PR was observed at CT scan (Figure 1). During the treatment a thrombosis of the inferior vena cava and hypercholesterolemia and hypertriglyceridemia occurred. Because of these adverse events and radiological benefit, chemotherapy was stopped and a close follow-up performed.

In March 2010, more than 4 months after the last cycle of first-line chemotherapy, PD of the liver metastases was observed at CT scan. A second-line chemotherapy with oxaliplatin and leucovorin/5-Fluorouracil (FOLFOX regimen) was proposed. After 6 cycles, in June 2010 a full-body CT scan showed PR in the liver (Figure 2). Due to toxicity (paresthesia G1, nausea G1, asthenia G1 and just one episode of neutropenia G3), the dose was reduced to 75% of the initial dose and chemotherapy kept on for further 6 cycles, until October 2010 when PD occurred (Figure 2). A third-line chemotherapy with irinotecan and fluoropyrimidines was advised and 3 cycles were delivered from December 2010 to January 2011. Due to further clinical PD, the patient died in February 2011.

Case 3

In March 2007, a 41 year-old Caucasian man suffering from abdominal pain underwent an abdominal CT scan showing a neoplasm of the pancreatic head with multiple liver metastases and thrombosis of the mesenteric vein. Histological examination of a hepatic biopsy concluded for metastases of G3 NEC, Ki-67 70%, high expression of somatostatin receptors (90%) and positive staining for chromogranin A (20%). Disease staging was completed by an SRS showing high uptake in the pancreatic head and bilateral hepatic lesions.

Due to the high proliferation index, a 3-drug first-line chemotherapy with Epirubicin, Cisplatin and 5fluorouracil (ECF regimen) was recommended. In June 2007 the chemotherapy was started, producing PR after the first 3 cycles and SD after six cycles.

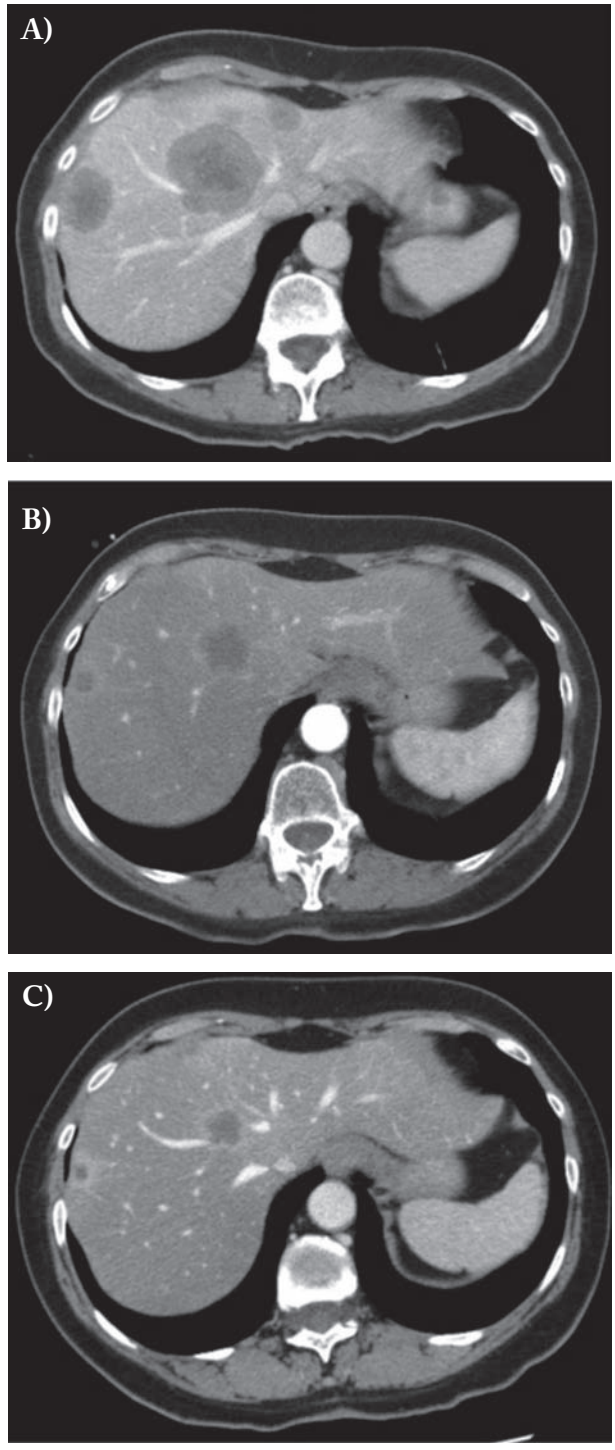

Figure 1. Case 2: response to first-line chemotherapy. Computed tomography (CT) scan following 6 courses of Carboplatin/Etoposide showing a huge hepatic partial response from June 2009 (A) to July 2009 (B), and then to September 2009 (C).

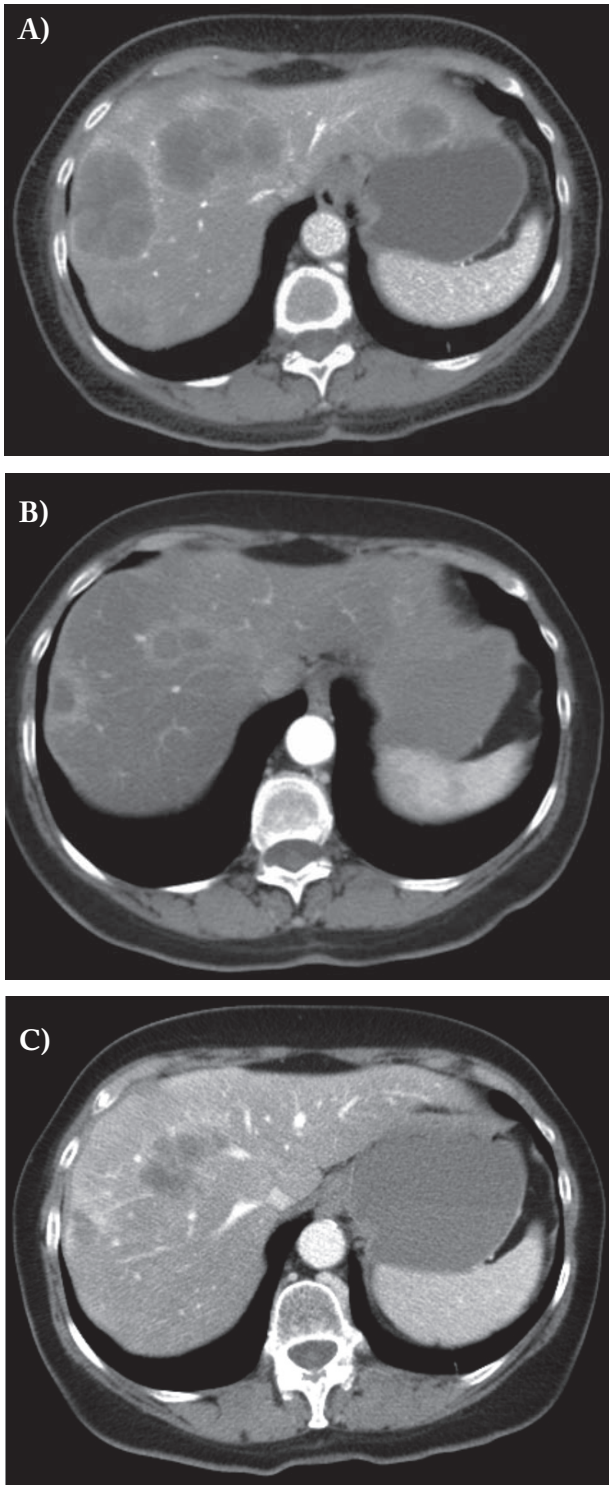

Figure 2. Case 2: response to second-line chemotherapy. Computed tomography (CT) scan following 6 courses of FOLFOX from March 2010 (A) to June 2010 (B) revealing that hepatic lesions were clearly decreased in size. Evidence of progression disease in November 2010 (C).

In November 2007, because of the clear response to chemotherapy, histological overexpression of somatostatin receptors and high uptake at SRS, a peptide receptor radionuclide therapy (PRRT) with 177Lu-Dotatate was carried out resulting in a partial response across all sites of disease. In May 2008, about 6 months after the end of ECF first line-therapy, an abdominal CT scan showed PD in both pancreas and liver with extensive mesenteric venous thrombosis involving the splenic vein. A second-line chemotherapy with gemcitabine and oxaliplatin (GEMOX regimen) was performed for 8 cycles. Two subsequent radiologic restagings showed PR of both pancreatic and hepatic lesions with improvement in the mesenteric and splenic venous thrombosis. GEMOX was stopped after a total of 8 cycles due to mild neurotoxicity.

After a further restaging performed in January 2009, showing persistence of response, the patient underwent hepatic trans-arterial embolization (TAE) and then, in June 2009 because of PD, was recommended a third-line chemotherapy with metronomic capecitabine. Due to further PD, the patient died in September 2010.

Discussion

Gastroenteropancreatic NECs are characterized by aggressive behavior and fast tumor growth. In most cases, diagnosis occurs at an advanced stage and chemotherapy represents the main therapeutic option, although the prognosis remains very poor. Based on retrospective literature data and similarities with SCLC, GEP-NEC patients usually receive CDDP/CBDCA + E chemotherapy as first-line treatment.

In a randomized phase III trial the combination of CDDP and E in SCLC patients proved superior to a 3-drug anthracycline-containing combination (specifically, cyclophosphamide, epirubicin and vincristine) (8). So, the main guidelines recommend the use of a platinum-based chemotherapy, either CDDP or CBDCA, in a first-line setting for SCLC (9-10). Actually, a meta-analysis of individual data, including four trials to a total of 663 patients, did not show any difference in either OS (9.6 vs 9.4 months) or PFS (5.5 vs 5.3 months) between CDDP-based versus CBDCA-

based therapy. In terms of toxicity, CBDCA-based regimens resulted as being more myelotoxic while CDDP-based regimens more clinically toxic (11).

In our case series, 2 out of 3 patients had been treated with a first-line CBDCA/E doublet and the third one with a CDDP-based triplet (ECF).

Despite good chemosensitivity, the risk of relapse of SCLC is very high and topotecan, orally or intravenously, is recommended as second-line chemotherapy (12,13). By contrast, the role of a second-line chemotherapy in GEP-NECs has not yet been clarified.

In a French retrospective study, 19 assessable Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 patients with NEC were reported to have undergone an effective and safe second-line chemotherapy [FOLFIRI regimen (irinotecan and leucovorin/5fluorouracil)] after failure of a platinum/etoposide combination: 62% overall response rate (ORR) and 18 months OS (14). Data from a Swedish retrospective trial, combining temozolomide and capecitabine +/- bevacizumab as second-line chemotherapy, regardless of MGMT (O6-methylguanine-DNA methyltransferase) methylation status, are similar: 71% ORR and 22 months OS (15).

It is noteworthy that in solid tumors, the likelihood of responding to subsequent treatment is strongly conditioned by the best response to the first-line chemotherapy and by the time interval between completion of the first-line and the beginning of the second-line treatment. Reintroduction of the same therapy - and specifically a platinum-based chemotherapy - is widely used in clinical practice. It is in fact possible to recognize three main categories of platinum-sensitive patients: "refractory" when PD occurs on treatment, "resistant" when the progression-free interval is lesser than 3 months, and "sensitive" when PD occurs after a lasting response (>3 months). For "sensitive patients", in particular those with >6 months' response, reintroduction of the same regimen is an option (10). Ovarian cancer is an emblematic case, in which four groups of patients are recognized: "platinum-refractory", "platinum-resistant", "partially platinum-sensitive" and "platinum-sensitive" patients (GCIG-Gynecolgical Cancer Intergroup Consensus) (7).

In the NORDIC NEC study by Sorbye *et al.*, aimed at identifying predictive and prognostic factors in advanced GEP-NECs, rechallenge of CDDP/CBDCA and E after a treatment break (usually for at least 3 months) was given to 29 patients, resulting in a response rate of 15% and 27% SD (26 assessable patients) (16).

The choice of a platinum derivative at the time of rechallenge should be based on the different toxicity profile of the platins and on the cumulative toxicity related to the first-line agent (11, 17). Oxaliplatin, differing from other platins in its mechanism of action and mechanism of resistance, is potentially effective in tumors with intrinsic or acquired resistance to cisplatin and carboplatin (18).

Oxaliplatin presents a different good safety profile from other platinum derivatives. Cisplatin is characterized by ototoxicity, emesis, nephrotoxicity and gastrointestinal toxicity, and carboplatin by myelotoxicity (11). Oxaliplatin is commonly well-tolerated and its main limiting toxicity is cumulative neurotoxicity (17).

The role of oxaliplatin is well-recognized in gastroenteropancreatic adenocarcinomas (colon, stomach and pancreas) (19-23). Oxaliplatin, in combination with fluoropyrimidines, is indicated for the management of colon adenocarcinoma in both the adjuvant and the metastatic settings (19-20). In advanced gastric cancer, cisplatin may be substituted with oxaliplatin as demonstrated by two randomized trials (21-22). More recently, the FOLFIRINOX regimen (5fluorouracil, irinotecan and oxaliplatin) compared to gemcitabine alone in metastatic pancreatic adenocarcinoma showed benefit for the first time in terms of OS as well (23).

Our patients had two pancreatic and one colon NEC, with a Ki-67 between 40 and 70% (42%, 55% and 70%, respectively); all of them experienced PR as best response with the first-line platinum-based chemotherapy and started the second-line after an interval of more than 3 months, so they may be considered platinum-sensitive.

With regard to the Ki-67 value, in the Scandinavian NORDIC study the response rate to first platinum-chemotherapy was significantly lower when Ki-67 was <55% (15% versus 42%), but the authors themselves conclude that this cut-off should be interpreted carefully (16).

In our case series, oxaliplatin was combined with different drugs, including capecitabine, 5fluorouracil

or gemcitabine. The schedules and doses were similar to those commonly used in the treatment of adenocarcinoma of the gastro-intestinal tract and, globally, oxaliplatin-based treatment was well-tolerated. In all of them the best response to subsequent oxaliplatin-therapy was RP and the response duration was ≥6 months.

The XELOX regimen was investigated in an Italian multicenter study with a mixed population of NET/NEC. In this study, 13 out of 40 patients had previously untreated NECs, in which 23% RR, 4 months' time to progression (TTP) and 5 months' OS were observed. In view of these disappointing results, the XELOX regimen is not recommended by the authors themselves as first-line chemotherapy for NECs (24). However, just 5 out of these 13 patients had a NEC which had certainly arisen in the gastro-intestinal tract (1 in the small bowel and 4 in the pancreas) while the value of Ki-67 was not available in any patient. Thus, we believe these findings are not sufficiently conclusive to deter further investigation of oxaliplatin in the management of GEP-NECs, even in a first-line setting. On the other hand, in a Brazilian retrospective study, which included nine G3 NEC patients (Ki67 not assessed), there was no significant statistical association between RR and either tumor grade, primary site or line of XELOX administration (25). In 2013 at the ENETS annual conference, results of 21 patients (all G3 NECs) who had undergone oxaliplatin-based second-line therapy were reported. In this French retrospective analysis, oxaliplatin-based second-line therapy (mostly FOLFOX) after failure of a platinum/etoposide combination showed an interesting 29% PR (5/17 assessable pts) and 9.5 months' OS. The ki-67 was available for 18 pts and a value of >55% seemed to be correlated with a worse prognosis. Unfortunately, data regarding free-interval time between first- and second-line therapy are not available (26).

Conclusions

In patients with metastatic GEP-NECs progressing on first-line CDDP/CBDCA-based chemotherapy a well-established second-line therapy has not yet been assessed. Our case series suggests that oxaliplatin can be active in this setting. Based on this and on some data on activity, not only in second-line but also up-front, in accordance with the conclusions of Spada et al. (27) we consider that prospective trials with oxaliplatin-based chemotherapy in second-line or even in first-line are warranted in patients with metastatic GEP-NEC.

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