The efficacy of oxaliplatin, surufatinib, and camrelizumab on neuroendocrine carcinoma: a case report and literature review

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Background: Extra-pulmonary neuroendocrine carcinomas (EP-NECs) are rare, accounting for ~1/100,000 of NECs, aggressive neoplasms and poor prognosis. Sometimes, a non-neuroendocrine component is also accompanying these EP-NECs. Curative surgery is suggested for early stage patients while system chemotherapy and locoregional radiotherapy are considered for advanced inoperable disease. Nonetheless, there was lack of standard second-line treatment strategy. Herein, we report a case of NEC involving a large cell neuroendocrine carcinoma (LCNEC) and adenocarcinoma of the gallbladder treated with a surufatinib-containing regimen in the second-line treatment setting and establish the efficacy of this regimen in the treatment of EP-NECs.

Case Description: A 58-year-old male presented with symptoms such as distension in the upper right abdomen and a palpable mass. The abdominal magnetic resonance imaging (MRI) scan showed a giant soft tissue mass in the left lobe of the liver, and liver biopsy suggested LCNEC with a non-neuroendocrine (NNE) component. Based on the available literature, a first-line therapy of oxaliplatin + gemcitabine + camrelizumab + apatinib was started initially; however, there was rapid tumor progression. Thus, a second line of treatment was started, where apatinib was replaced with surufatinib, which was given along with oxaliplatin and camrelizumab and continued for seven complete cycles. The patient was re-examined with MRI, which showed a significant decrease in tumor size. And a partial response was achieved. Main adverse events included hand and foot numbness, hypertension, proteinuria, hematuria, and hyperthyroidism. The patient underwent surgery after the second line of treatment and the post-operative pathology report revealed the presence of LCNEC and adenocarcinoma of the gallbladder. Two months later, re-examination result showed no tumor recurrence.

Conclusions: As yet, the criteria strategy for unresectable EP-NECs to improve survival outcomes is scarce. EP-NECs are badly in need of effective second-line therapy to carry out survival benefits after resistance to first-line regimen. The case report demonstrated that a surufatinib-containing regimen including oxaliplatin and camrelizumab could be an effective treatment strategy for the second-line treatment of EP-NECs. Furthermore, this strategy is well tolerated and treatment-related toxicity are manageable. More clinical trials are warranted to further confirm the efficacy.

Keywords: Surufatinib; large cell neuroendocrine carcinoma (LCNEC); adenocarcinoma; extra-pulmonary neuroendocrine carcinoma (EP-NEC); case report

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Introduction

Neuroendocrine carcinomas (NECs) are a poorly differentiated and highly aggressive form of neuroendocrine neoplasm (NEN) (1,2). While small cell and large cell lung NECs are well characterized, very limited data is available regarding extra-pulmonary neuroendocrine carcinomas (EP-NECs) (2). Although rare (adjusted annual incidence of ~1/100,000), EP-NECs can occur in various organs, with the majority occurring in the gastroenteropancreatic NEC (GEP-NEC), constituting approximately one-third of all EP-NEC cases (1). Patients are generally diagnosed with metastatic disease with a survival of approximately 5 months (3). Generally, these poorly differentiated GEP-NECs resemble small cell or large cell carcinomas of lungs or other sites and have been sub-classified as per the tumor cell morphology into small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC) (2,4).

A study has shown that besides harboring the neuroendocrine (NE) component, approximately 40% of GEP-NECs also carry a non-neuroendocrine (NNE) component (5). Thus, apart from the SCNEC and LCNEC, the World Health Organization (WHO) has added another subtype of GEP-NEC known as mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) (6). It was decided that both NE and NNE components should constitute at least 30% each of the total tumor mass for a GEP-NEC to be classified as MiNEN, assuming that the tumor prognosis is affected by a minor NE component (<30%) in an NNE malignancy (5,7). However, recent studies have shown that the presence of more than 10% of a NE component may also be clinically relevant to the prognosis of such tumors (8,9).

Due to the lack of any definitive therapy, the treatment for EP-NEC follows the treatment paradigm of pulmonary NEC. Therefore, surgery remains the cornerstone of EP-NEC in cases of localized disease and etoposide plus cisplatin (EP) and irinotecan plus cisplatin (IP) as a systemic therapy in the first-line setting in advanced EP-NECs that are not amenable to curative surgery. Recently, an open-label phase 3 randomized clinical trial had confirmed the efficacy of EP and IP in the cohort of 170 patients with advanced NEC of digestive system, prolonging median progression-free survival (PFS) to 5.6 months (range: 4.1–6.9 months) and 5.1 (range: 3.3–5.7 months) months in the EP arm and IP arm respectively. Simultaneously, the common adverse events were manageable, including neutropenia, leukocytopenia and febrile neutropenia (10). The alternative second-line treatments included fluorouracil-base regimen plus oxaliplatin, fluorouracil-base regimen plus irinotecan and temozolomide monotherapy or combined with capecitabine after the GEP-NECs having a relapse, while those patient had a median PFS of 2–6 months with gastrointestinal toxicity (11). However, there has been no consensus for second-line treatment following progression of the disease (3). This necessitates the development of new treatment strategies that can benefit patients with EP-NEC.

In this regard, various clinical and preclinical studies have demonstrated the synergistic effect of platinum-based therapy in combination with programmed cell death ligand 1 (PD-L1) antibody or anti-programmed cell death protein-1 (PD-1) inhibitors. These mechanistic studies have demonstrated the synergistic action of the two drugs in regulating PD-L1 expression leading to cell death, thereby delaying tumor growth (12,13). Surufatinib is a small molecule inhibitor that inhibits vascular endothelial growth factor receptor 1-3 (VEGFR1-3), fibroblast growth factor receptor-1 (FGFR1), and colony-stimulating factor-1 receptor (*CSF-1R*). By inhibiting these receptors, surufatinib targets both angiogenesis and the tumor's immune evasion. Clinical studies have shown a significant decrease in tumor growth with surufatinib in patients with advanced and well-differentiated pancreatic and extra-pancreatic neuroendocrine tumor (NET), suggesting a potential new approach to the treatment of LCNEC (14,15). Herein, we report a case of gallbladder LCNEC treated with a surufatinib-containing regimen in the second-line setting, demonstrating the significant clinical efficacy of surufatinib in the treatment of EP-NECs. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4789/rc).

Case presentation

A 58-year-old male complained of distension in the upper

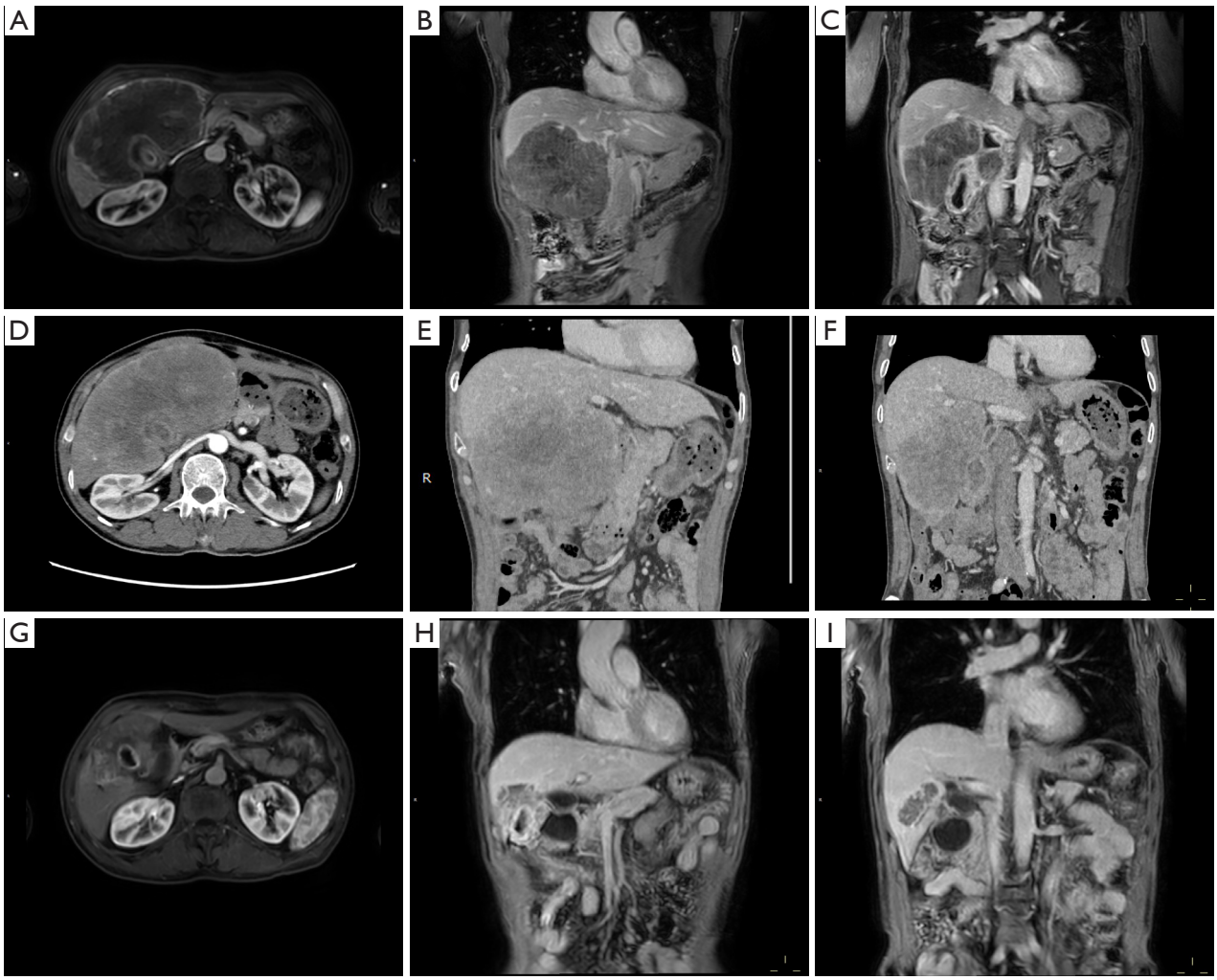

Figure 1 Clinical images. (A-C) MRI with contrast before first-line treatment showed a giant low-enhancement tissue mass (approximately 14.8×7.4 cm) in the left lobe of the liver with an unclear boundary between the lesion and the gallbladder. (D-F) Enhanced CT with contrast after first-line therapy shows a huge soft tissue mass (about 17.0×10.3×11.5 cm) in the left lobe of the liver, which is larger than before, protruding the liver capsule and invading the colonic hepatic flexure. (G-I) MRI with contrast after a second-line treatment regimen containing surufatinib shows a significant decrease in tumor size, measuring about 9×6.8×6 cm. MRI, magnetic resonating imaging; CT, computed tomography.

right abdomen along with the presence of a palpable mass and hence was admitted to the local hospital on the 1st of August 2021. The patient had a history of type 2 diabetes mellitus and was taking metformin, glibenclamide (one tablet, three-times a day), and pioglitazone dispersible tablets (15 mg, three-times a day) to maintain his blood glucose control. Apart from diabetes, the patient had no history of other diseases or tumors or other family histories of genetic disorders.

After admission, the patient had undergone abdominal magnetic resonance imaging (MRI) with contrast. The MRI showed a giant soft tissue mass of approximately 9.5×12×9.7 cm in the left lobe of the liver with an unclear boundary between the lesion and the gallbladder, and multiple small lymph nodes were observed beside the abdominal aorta. One month later, the patient was admitted to the Department of Hepato-Pancreato-Biliary Surgery at the China-Japan Friendship Hospital. Abdominal MRI and positron emission tomography-computed tomography (PET-CT) showed a liver lesion with increased tumor size

(14.8×7.4 cm) (*Figure 1A-1C*). Furthermore, higher levels of tumor markers, such as cancer antigen 19-9 (CA-19-9), carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE), were observed (512.00 U/mL, 93.40 ng/mL, and 56.00 ng/mL, respectively). The liver biopsy results revealed poorly differentiated carcinoma with necrosis. Furthermore, immunohistochemistry (IHC) was conducted to consider LCNEC with focal adenocarcinoma differentiation. IHC was also performed to investigate the expression of proliferation and other tumor markers, which revealed that the Ki-67 index was 80%. The expressions were negative for chromogranin (CgA), synaptophysin (Syn), insulinoma-associated protein-1 (INSM1), as well as hepatocyte and retinoblastoma (Rb) loss of expression. Markers such as neural cell adhesion molecule (also called CD56), P53 (nonsense mutation pattern), CEA focal, alcian blue/periodic acid-Schiff (AB-PAS; foci of glandular differentiation), and periodic acid-Schiff with diastase (D-PAS; foci of glandular differentiation) showed positive expressions. The patient was diagnosed with stage III.

Since the tumor size was large and invaded the hepatic artery, surgery was contra-indicated. To balance the patient's safety and treatment efficacy, first-line therapy was started with gemcitabine and oxaliplatin (GEMOX) as well as targeted therapy combined with immunotherapy. The patient was treated with 150 mg of oxaliplatin day 1, 1,600 mg of gemcitabine day 1, 200 mg of camrelizumab day 1, and 250 mg of apatinib orally once daily. A few days later, to prevent the toxic effects of chemotherapy, only 200 mg of camrelizumab and oral apatinib were continued. Furthermore, computed tomography (CT) with contrast was performed to examine the chest and abdomen on the 8th of October 2021. The CT scan showed progression in the left lobe of the liver with a huge soft tissue mass (about 17.0×10.3×11.5 cm) protruding the liver capsule and invading the colonic hepatic flexure. Angiogenesis was observed around the tumor, adjacent to the ascending colon and gallbladder (*Figure 1D-1F*). Thus, the PFS of the patient with first-line therapy was only 1.17 months.

Due to progression of the tumor observed with a CT scan, the patient was admitted to the Department of Integrative Oncology at the China-Japan Friendship Hospital, and a second-line treatment where apatinib was replaced with surufatinib was initiated and further observed. The treatment regimen included 150 mg of oxaliplatin day 1, 200 mg of camrelizumab day 1, and 250 mg of surufatinib orally once daily, every 21 days. The patient completed a total of seven cycles of treatment and was re-examined using abdominal MRI and CT scans. The scans showed a significant decrease in tumor size that measured about 9×6.8×6 cm, thereby indicating a partial response (*Figure 1G-1I*). Serum tumor markers such as CA-199, CEA, and NSE were re-investigated following second-line treatment. The results revealed a remarkable decrease in CA-199, CEA, and NSE (51.10 U/mL, 9.19 ng/mL, and 15.00 ng/mL, respectively).

The patient experienced adverse reactions such as hand and foot numbness due to the large cumulative dose of oxaliplatin. Thus, oxaliplatin was discontinued and only camrelizumab monotherapy was continued further. Other adverse reactions observed during the treatment included hypertension, proteinuria, hematuria, and hyperthyroidism. Due to the significant tumor shrinkage during the second-line treatment with surufatinib + oxaliplatin + camrelizumab, the hepatobiliary surgeons considered that the patient had an opportunity to undergo surgery. Surufatinib was discontinued for preoperative preparations and to evaluate the indications required for the surgery. Following these preparations, the patient underwent partial hepatectomy + cholecystectomy + right hemicolectomy under general anesthesia on the 18th of April 2022.

Post-operatively, the presence of mixed adenocarcinoma of gallbladder and LCNEC (size 8×7×3.5 cm) with necrosis, histiocyte aggregation, fibrous tissue hyperplasia, and chronic inflammatory cell infiltration was observed. The pathology results showed that LCNEC (NE component) and adenocarcinoma of the gallbladder (NNE component) constituted 90% and 10%, respectively (*Figure 2*). No metastasis was observed in the pericolonic lymph nodes (0/13). IHC revealed the expression of CD56 (+), CgA (–), Syn (–), INSM1 (–), Ki-67 (MIB-1, 80%+f), P53 (+, nonsense mutation), Rb (–, expression loss) for LCNEC cells and CEA (+), CD56 (–), CgA (–), Syn (–), P53 (+, missense mutation), Rb (+), Ki67 (MIB-1, 50%), AB-PAS (+, focus), and D-PAS (+, focus) for adenocarcinoma cells (*Figure 3*). PIK3CA p.Glu545Lys mutation was detected, while the IHC for PD-L1 test results showed positive PD-L1 expression. At present, the patient has received R0 resection, and is receiving postoperative adjuvant therapy with capecitabine + PD-1 inhibitor. Two months later, MRI showed no definite sign of tumor recurrence (*Figure 4*).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and

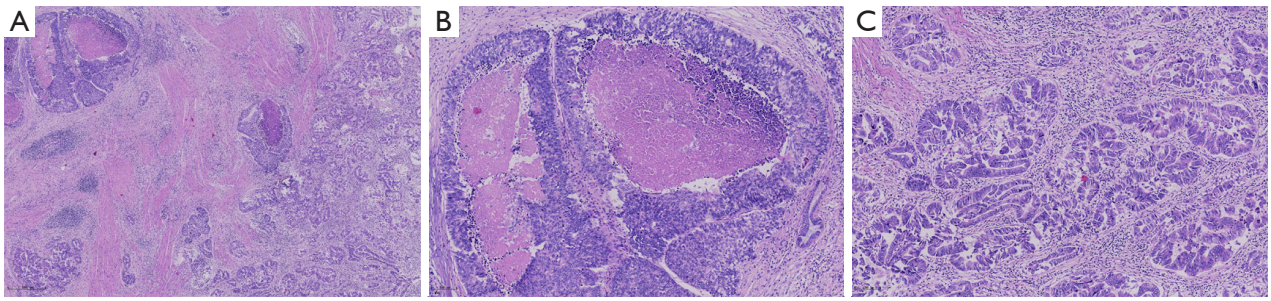

Figure 2 Postoperative pathology. (A) Both components were intermingled with large cell neuroendocrine carcinoma and adenocarcinoma (left large cell neuroendocrine carcinoma, right lower adenocarcinoma) (hematoxylin and eosin, scale bar: 500 μm, original magnification ×40); (B) large cell neuroendocrine carcinoma (hematoxylin and eosin, scale bar: 100 μm, original magnification ×200); (C) adenocarcinoma (hematoxylin and eosin, scale bar: 100 μm, original magnification ×200).

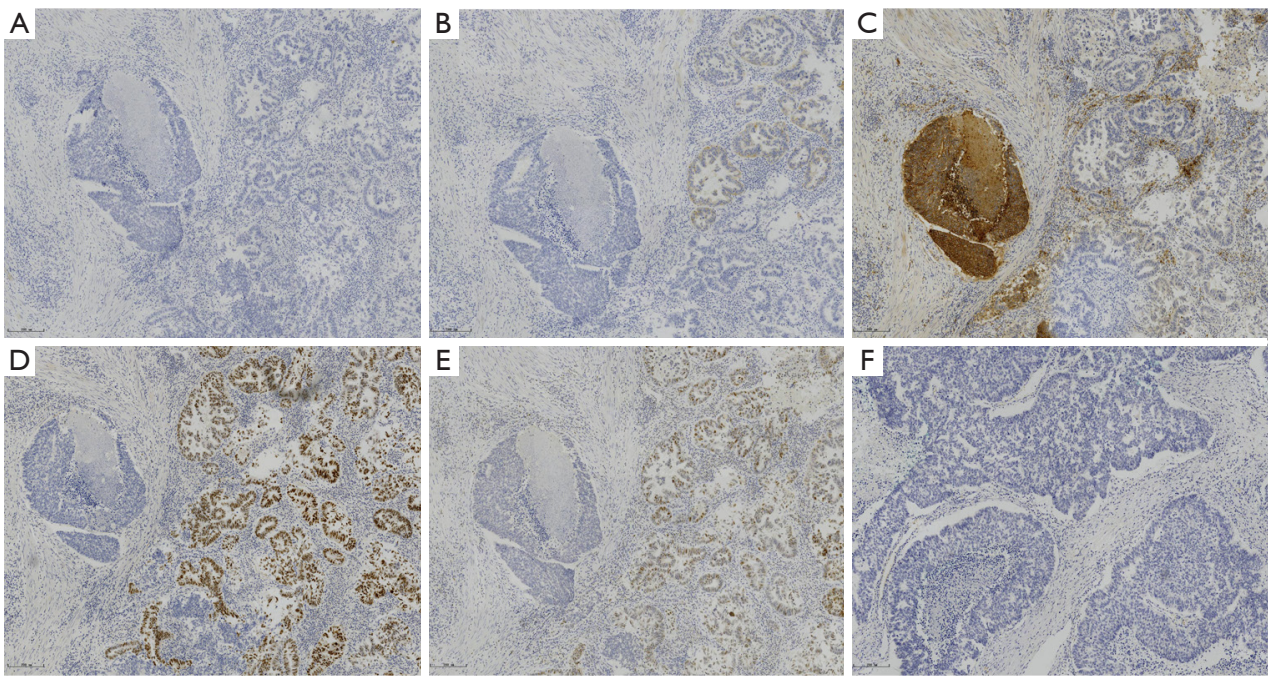

Figure 3 Postoperative immunohistochemistry. (A,B) The tumor cells were negative for CgA and Syn (IHC, original magnification ×100). (C) The tumor cells were positive for CD56 (IHC, original magnification ×100). (D) P53, adenocarcinoma missense mutation (diffuse strong +, right), LCNEC nonsense mutation (all negative, left) (IHC, original magnification ×100). (E) Rb, no deletion in adenocarcinoma (right), deletion in LCNEC (left) (IHC, original magnification ×100). (F) The tumor cells were negative for INSM1 (IHC, original magnification ×100). Scale bar: 200 μm. IHC, immunohistochemistry; LCNEC, large cell neuroendocrine carcinoma.

accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

EP-NECs including GEP-NECs and its subcategory LCNECs are rare and highly aggressive neoplasms (3). Owing to the rare nature of EP-NEC, it has a very low incidence rate, which limits the scope of therapeutic strategies and possible clinical trials. In our study, the initial liver biopsy revealed GEP-NEC concurrent with adenocarcinoma as NEC with NNE. Although the NNE

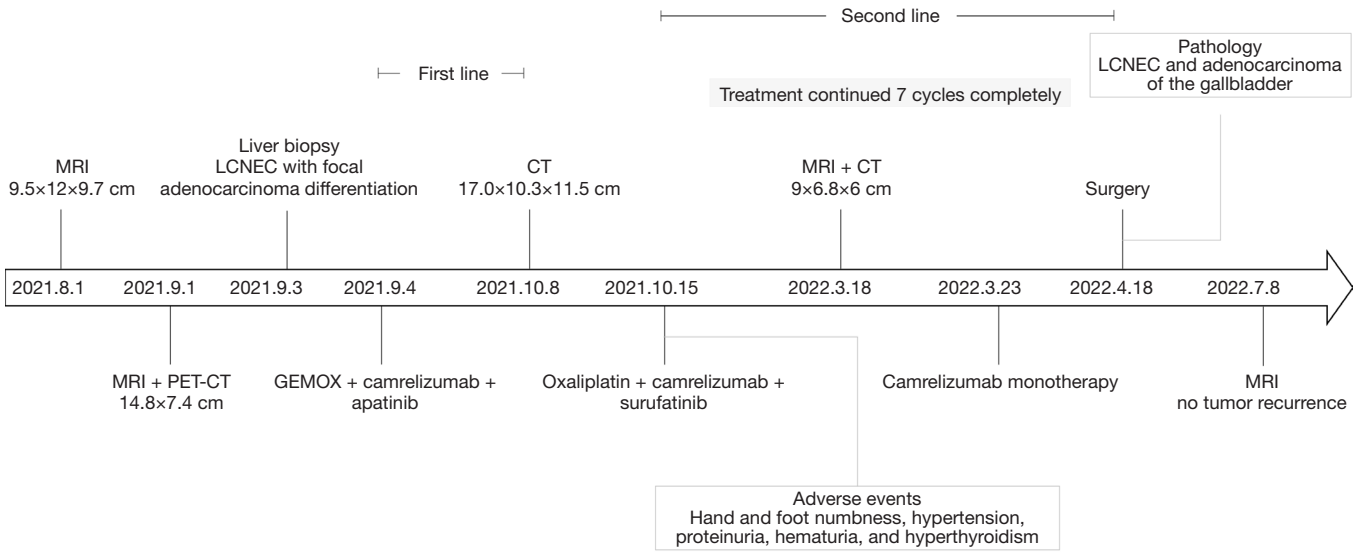

Figure 4 Timeline of the patient's treatment. MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; LCNEC, large cell neuroendocrine carcinoma; GEMOX, oxaliplatin + gemcitabine; CT, computed tomography.

adenocarcinoma component could be diagnosed from the initial biopsy, the primary tumor site could only be identified using surgically-resected samples, which increases the difficulty in identifying an appropriate treatment strategy (7). Hence, there remains a dilemma around whether therapy should be selected to target NEC or NNE. In general, such decisions are taken on a case-by-case basis. The postoperative pathology report of our patient revealed the presence of LCNEC (comprising 90% of the total tumor mass), which is a rare, aggressive, and fast-growing subgroup of NEC.

In our study, the patient presented with a giant mass limited to only liver tissue, and hence, we determined to perform surgery in this case. However, due to the large size of the tumor, there was a risk in performing surgery, and we opted for systemic treatment instead. Owing to the lack of any definitive therapy for LCNEC, the standard first line of treatment for these patients remains platinum/etoposide-based adjuvant chemotherapy with curative surgery, based on the available literature (3,16). A recent retrospective analysis of 50 patients with GEP MiNEN showed a median overall survival of 31 months (1–104 months) with chemotherapy using platinum/etoposide, palliative chemotherapy, and 5-fluorouracil based chemotherapy, supporting the use of chemotherapy for such cases (17). However, 28 patients had died at the end of the follow-up period. Another study demonstrated a median overall survival of 12.2 months (5.9–33.9) in patients with MiNEN treated with adjuvant chemotherapies (18).

There is a lack of phase III data for the second-line treatment of EP-NEC and more reference is made to the data in pulmonary neuroendocrine carcinomas (P-NECs). For the treatment of EP-NECs, EP and IP remain the standard first-line chemotherapy regimens (10). Furthermore, other combinations of drugs such as 5-fluorouracil, leucovorin, oxaliplatin combination regimen (FOLFOX), folinic acid, 5-fluorouracil and irinotecan (FOLFIRI), or capecitabine plus temozolomide (CAPTEM) can also be used (16). A multicenter, retrospective study showed a promising effect of oxaliplatin-based chemotherapy for the treatment of patients with gastroenteropancreatic NETs, with a disease control rate of 80% and a PFS of 8 months (19). Furthermore, several phase II clinical trials have demonstrated the significant effect of the GEMOX regimen in the treatment of different solid tumors and hematological neoplasms with tolerable toxicity (20,21). Furthermore, Park *et al.* demonstrated the efficacy and possible mechanism of action of oxaliplatin or cisplatin monotherapy in combination with anti-PD-1 *in vitro* and *in vivo*. Their results revealed a delay in tumor growth and prolonged survival that might be due to the synergistic action of oxaliplatin or cisplatin with anti-

PD-1 by increasing the levels of calreticulin at the cell surface and major histocompatibility complex class I, thereby augmenting the immunogenic cell death by up-regulating cell surface expression of PD-L1 *in vivo* (13). A recent phase 2 multicenter study has shown a significant objective response rate (ORR) of 75% with camrelizumab, a PD-1 inhibitor, combined with GEMOX in patients with biliary tract cancer (22). Moreover, a case report by Liu *et al.* [2022] showed a potential effect of combinatorial therapy of GEMOX and anti-PD-1 therapy in patients with unresectable gallbladder cancer (23). VEGF is known to play a key role in tumor angiogenesis, and VEGF signaling is the primary rate-limiting step in this process. Therefore, several vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) have been approved in several solid tumors (24). Apatinib is one such VEGF-TKI that has shown promising results in the treatment of gastric cancer (25). In line with these results, treatment with apatinib as second-line therapy in Chinese patients with advanced hepatocellular carcinoma resulted in an ORR of 10.7% (26). Various studies have also demonstrated the promising anti-tumor activity of apatinib combined with camrelizumab in multi-tumor types, with an ORR of 34.3% as first-line therapy and 10.7–22.5% as second-line therapy (27-29).

Thus, based on the available literature, a treatment armamentarium was selected to transform our patient into surgery and he was put on GEMOX combined with apatinib and camrelizumab as first-line therapy. Despite the promising results reported in the literature, we observed a PFS of only 1.17 months in this case, confirming the progressive disease of the patient. Previous studies have demonstrated that although patients with EP-NEC are sensitive to platinum/etoposide-containing regimes, these treatments have demonstrated only a limited duration of tumor control and overall survival of the patients. Several clinical trials that are treating EP-NEC patients using different combinations of drugs are underway; however, there are currently no standard second-line treatment guidelines available (5,20).

Therefore, to address the dilemma of treating NEC with NNE, we reconsidered the treatment target for NEC. Given the shorter PFS and no reduction in tumor size with first-line therapy, surufatinib was considered for second-line therapy. Surufatinib is a TKI with a unique mechanism of action of simultaneously inhibiting angiogenesis (VEGFR1-3 and FGFR1) as well as tumor-immune evasion [macrophage colony-stimulating factor 1 (CSF1) receptor], thereby resulting in enhanced antitumor activity. Two recent phase III clinical trials have demonstrated a significant response to surufatinib, with a prolonged median PFS of 10.9 months (range: 7.5–13.8) in patients with pancreatic NET and a median PFS of 9.2 months (range: 7.4–11.1) in patients with extra-pancreatic NET (14,15). Surufatinib has also been approved for well-differentiated NEN, and a current phase III trial of surufatinib combined with PD-1 focusing on NEC is in progress. In this regard, a phase II trial has also shown a significant efficacy of second-line therapy with surufatinib combined with toripalimab, a PD-1 antibody, prolonging the PFS by 4 months (range: 1.31–unknown) in 80% of patients with EP-NEC (30). In another phase II study in patients with biliary tract cancer, surufatinib has shown a PFS of 3.7 months and median OS of 6.9 months when given as second-line therapy (31). It is speculated that surufatinib exerts an immunomodulatory effect by decreasing M2 tumor-associated macrophages (TAMs) and increasing M1 TAMs, which might be responsible for enhancing the antitumor activity of surufatinib when combined with anti-PD-1/PD-L1 antibody. Furthermore, previous preclinical and clinical studies have shown that a combination of surufatinib/oxaliplatin-based chemotherapy with PD-L1 antibody or anti-PD-1 resulted in significant clinical benefits in patients with advanced solid tumors (13,32).

In our study, treatment of EP-NEC with surufatinib combined with oxaliplatin and camrelizumab in a second-line setting not only decreased the tumor size but also significantly prolonged survival, thereby resulting in a partial response. Tumor markers such as CA-199, CEA, and NSE also showed a marked decrease, indicating the beneficial effect of adding surufatinib to existing chemoimmunotherapy regimens. Thus, the advanced NEC transformation was successfully achieved, making the tumor resectable. In addition, positive PD-L1 expression indicates that the patient might benefit from immunochemotherapy treatment. Future long-term studies with a larger sample size would be required to validate the current findings and subsequent application of surufatinib-based regimens in clinical practice.

Conclusions

This study showed a significantly prolonged survival as a result of the effect of surufatinib combined with oxaliplatin and a PD-1 inhibitor for the second-line treatment of EP-NEC. Thus, a surufatinib-containing regimen could be a potential treatment option for EP-NECs and patient tolerated treatment well. However, further studies are

warranted. The findings of this study also highlighted that targeting the particular component of NEC with NNE could be a deciding factor for the prognostic outcomes in such cases.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4789/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4789/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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