Oncological management of advanced neuroendocrine tumours (Review)

PAWEŁ GUT

Department of Endocrinology, Metabolism and Internal Diseases, Poznan University of Medical Sciences, Poznań 60-355, Poland

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Abstract. The oncological principles of managing patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) depends on a number of factors and requires a multidisciplinary approach. Recent data have provided additional therapeutic options, including biotherapy, traditional chemotherapy and novel targeted agents. Somatostatin analogues (SSAs) inhibit multiple cellular functions, including secretion, motility and proliferation. Interferon appears to act through several mechanisms, with antisecretory effects, immunomodulatory effects and antiproliferative functions, the latter inhibiting direct growth or attenuating angiogenesis. Opinions on when to commence chemotherapy for well differentiated GEP-NETs varies among experts. In previous years, reserving chemotherapy for patients with progressive disease (well differentiated, inoperable and/or metastatic GEP-NETs) was reasonably well argued for. Most well differentiated endocrine tumours are richly vascular and many express vascular endothelial growth factor (VEGF) receptors. In a xenograft model of a human carcinoid, treatment with an anti-VEGF monoclonal antibody was revealed to inhibit tumour growth and metastasis. As the role of angiogenesis and hypoxic-associated factors appears to be associated with tumour aggressiveness, strategies using agents which target angiogenesis have been developed. Mammalian target of rapamycin (mTOR) is a conserved serine-threonine kinase that regulates the cell cycle and metabolism in response to environmental factors. In addition, mTOR inhibition suppression was demonstrated to suppress NET growth. Each patient requires an individual approach to the choice of therapy, which should be selected depending on the severity of disease.

Correspondence to: Dr Paweł Gut, Department of Endocrinology, Metabolism and Internal Diseases, Poznan University of Medical Sciences, 49 Przybyszewski Street, Poznań 60-355, Poland
E-mail: gutpj@poczta.onet.pl

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1. Introduction

The oncological principles of management in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) depend on a number of factors and require a multidisciplinary approach. Curative surgery is rarely possible in patients with metastatic disease, and other approaches are therefore necessary. Antiproliferative treatment decisions depends on a number of key factors: Firstly, the origin of the primary tumour; secondly, the histological differentiation and tumour grade, and finally on the aggressiveness and proliferative capacity of the tumour. Unlike other solid tumours in the digestive tract, wait-and-see strategies can often be adopted in GEP-NET patients. It is associated with the highly differentiated nature of neuroendocrine tumors and the often slow progression of the disease. Recent data have changed the therapeutic options and the results of biotherapy, traditional chemotherapy and new targeted agents have opened an exciting volley of therapies in this ever changing field. Well-coordinated international multicentre trails have afforded the opportunity of pooling resources in a field of rare tumour disease and to respond to interesting clinical questions.

2. Biotherapy

Somatostatin analogue treatment in GEP-NETs. Somatostatin and its analogues (SSAs) inhibit multiple cellular functions, including secretion, motility and proliferation. Its action is mediated by five specific somatostatin receptors (sstr 1-5), which belong to the G protein-coupled receptor family. The five receptors bind the natural peptide with high affinity, but only sstr2, sstr3 and sstr5 bind the short synthetic analogues used to treat GEP-NET patients. SSAs have been used

successfully to treat functional GEP-NETs (e.g. carcinoid syndrome, VIP-omas) (1). The basis for the use of SSAs is the expression of somatostatin receptor subtypes in 80-90% of GEP-NETs according to autoradiographic or scintigraphic studies (2). The biological effects of SSAs occur in relation to receptor subtype interaction; inhibition of secretion appears to be largely mediated via the effects of the sstr2 subtype, and all commercially available SSAs have appreciable affinity for sstr2 (3,4). However, proliferation in endocrine tissue may be mediated via other receptor subtypes (5).

Anti-tumour effect of SSAs. The initial studies examining the antiproliferative role of SSAs are difficult to interpret due to: The heterogeneity of tumour types (site of origin, tumour histology, tumour load and type of metastatic disease); the use of different formulations and doses; the lack of objective tumour progression prior to treatment with SSAs, meaning that disease stabilisation may also be attributable to the slowly progressive natural history common to many GET-NETs, and until recently, the complete lack of any randomised study examining this question (6,7). Eriksson and Oberg collected data from 62 published studies or mini-series pertaining to treatment with octreotide: Tumour shrinkage was reported in only 10-20% of patients, but stabilisation of tumour growth for 8-16 months could be achieved in about half of the patients (8). Other data, mostly examining the efficacy of long-acting forms of SSAs, suggest that, overall, objective responses are rare (<10%) with reasonable disease stabilisation in up to 50% of patients (with a response duration of 10-25 months) (9). A phase III study comparing lanreotide with interferon, and their combination, showed a partial tumour response of only 4% for the lanreotide arm, whereas disease stabilisation was observed in 28% of patients (10). Disease stabilisation thereafter confirmed in two further reports, with rates of 46 and 16% for octreotide doses of 450 and 600 mg/day, respectively (11). Results appear to be similar for both functioning and non-functioning tumours (12). The publication of a randomized trial comparing Sandostatin-LAR 30 mg every 28 days to placebo provided a definitive answer to the antiproliferative effects of SSAs in patients with metastatic midgut disease (13). In third important trial, 85 patients were randomized to receive 30 mg Sandostatin-LAR or placebo. The median time to progression was significantly longer in the octreotide arm (14.3 months vs. 6 months) and the overall reduction in risk of tumour progression attributable to Sandostatin-LAR was 66% (HR 0.34). This effect was achieved via disease stabilization; there were no complete responses and only 1 partial response in treatment and placebo arms, respectively. The antiproliferative effect was visible in patients with or without carcinoid syndrome. At subanalysis, the most favourable outcomes were observed in patients with a small (<10%) hepatic tumour loadband in those whose primary tumour had been resected. These data broadly confirm that SSAs have a real antiproliferative effect and that they should be considered in patients with advanced carcinoid tumours. The published CLARINET study results, confirmed the antiproliferative effect of lanreotide. The study was participated by 204 patients with NEN G1 and G2 (Ki 67<10%), non-functioning with primary site in pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%) (14). The development of agents such as pasireotide, capable an if increased affinity to certain sstr subtypes (e.g., bi-specific sstr2 and sstr5, or multi-specific binding capacity), or chimeras capable of recognising both sstr2 and dopamine D2 receptors (D2 was also recently identified in GEP-NETs) (15). May prove more efficacious in antiproliferative terms. Indeed, the dopamine-somatostatin chimeric molecule, BIM-23A760, has been shown to be efficacious in the control of cell growth from primary cultures of human non-functioning pituitary adenomas in a multi-centre study (16). However, use of such agents appears to be cell specific as highlighted by a recent *in vitro* analysis (17).

3. Interferon

Interferon appears to act through several mechanisms, with antisecretory, immunomodulatory effects, and antiproliferative functions (18), the latter in relation to direct growth inhibition or the attenuation of angiogenesis. Data interpretation is hampered by the use of varying types of interferon (INF-α-2α, INF-α-2β and human leukocyte interferon HuINF-α-Le) combined with non-randomised heterogeneous studies in relatively small numbers of patients. Similarly to SSAs, the use of interferon in GEP-NETs with carcinoid syndrome has been found to be beneficial in controlling symptoms (60% reduction in flushes and diarrhoea, respectively) and biochemical tumour markers. However, objective tumour responses are rare. Disease stabilisation, with standard doses of 3-9 MIU three times weekly, is reported to occur in approximately 35% of patients, with a median duration of response of 32 months (19). Higher doses do not confer a therapeutic advantage. In a recent phase III trial 64 patients with documented progressive, unresectable, metastatic carcinoid tumours (>60% were midgut in origin) were randomized between 5-fluorouracil and streptozocin (day 1-5) and recombinant INF-α-2α (3MU, 3 per week) (20). The median PFS for chemotherapy was 5.5 months vs. 14.1 for IFN [HR: 0.75 (0.41-1.36)]. Overall survival, tolerance, and effects on carcinoid symptoms were not significantly different. A long-acting preparation (pegylated interferon, PEG-INF), which achieves constant plasma concentrations with fewer adverse events (which can include flu-like symptoms, fatigue, haematological toxicity, etc.) was recently compared to bevacizumab in a phase II trial, in patients with metastatic or unresectable carcinoid disease (21). Forty-four patients on stable doses of octreotide were randomly assigned to 18 weeks of bevacizumab or PEG-INF-α-2β. The results of PEG-INF-α-2β compared to bevacizumab respectively were as follows: 0 vs. 4 (18%) partial responses, 15 (68%) vs. 17 (77%) stable disease, and 6 (27%) vs. 1 (5%) progressive disease. The PFS rate after 18 weeks was 95% in bevacizumab vs. 68% on the PEG INF arm (22). Overall, the interferon was well tolerated. A major limitation of this study was the lack of documented disease progression in all patients randomized, thus results pertaining to disease stabilization could not be interpreted.

4. Chemotherapy

General principals. Opinions on when to commence chemotherapy for well differentiated GEP-NETs varies among experts. In years past, reserving chemotherapy for patients

with progressive disease (well differentiated, inoperable, and/or metastatic GEP-NETs) was reasonably well argued for. The slow natural progression of GEP-NETs in many patients allows for careful monitoring and the instigation of treatment once disease progression is documented. The definition of a well differentiated tumour will no doubt require clarification, as we have seen recently there is a difference between natural history and response to therapy according to tumour grade (above or below Ki-67 at 3%) (23). Is it therefore reasonable to adopt a wait-and-see attitude for patients with well differentiated grade 2 tumours (Ki-67 >3%). The anti-proliferative effects of SSAs would appear to be most applicable to grade 1 tumours, and the use of SSAs monotherapy (at least in GEP-NETs of midgut origin) in this setting may be reasonable, which reserves chemotherapeutic agents for documented progressive disease. Most experts would argue for early chemotherapy in patients with well-differentiated bulky disease at the outset or poorly differentiated tumours. Accurate histological classification is not always easy, as interobserver differences among pathologists are not uncommon (24). Guidelines to increase uniformity in this respect are required. The importance of accurate histology cannot be underestimated, and in cases where doubt exists, slides should be re-examined by several independent histopathologists. The use of the Ki-67 proliferation index has been helpful in distinguishing certain tumours and guiding treatment regiments. This marker is invariably high (>20%) in poorly differentiated lesions and identification of grade 3 GEP-NETs is usually reasonably simple. However, it may be difficult to choose appropriate therapy in cases where the histological architecture resembles a well differentiated tumour but there is a moderately elevated Ki-67 (3-20%) or borderline tumours, indeed, the gap between 3 and 20% may be too generous. Analysing biopsy samples, compared to larger operative specimens, poses special problems in performing estimates (25). The appraisal of proliferation indices and their relationship to treatment outcomes is required in future study protocols. Apart from histological differentiation, the type of chemotherapy has been largely based on the site of origin of the primary tumour. To date, this paradigm remains pertinent but may change in the future with the discovery of agents, cytotoxics or targeted therapies that are universally applicable to GEP-NETs.

New molecular predictors. Recent efforts have been made to try to determine molecular predictors of response to therapy. O-6-methylguanine-DNA methyltransferase (MGMT) deficiency, measured by immunohistochemistry, was found to predict a better response to temozolomide-based therapy (26). A further study in a group of 60 GEP-NET patients treated with chemotherapeutic agents a number or markers were found to be associated with response to individual therapies (including tyrosine kinase, Akt, thymidylate synthase (TS), phosphatase and tensin homologue (PTEN), Ki-67 and the hypoxic factor CA9 (27). These results demonstrate a number of new prognostic biomarkers in GEP-NETs, and in addition, response to chemotherapy was correlated with a simple panel of selected markers [such as CA9, Akt, PTEN, TS, and mismatch repair gene-human mutL homologue 1 (hLMH1)]. Tailoring therapies to suit individual patients should become possible as the molecular events associated with treatment responses are revealed.

5. Chemotherapy for well differentiated digestive GEP-NETs

Pancreatic. Apart from insulinomas, other pancreatic GEP-NETs are frequently associated with metastatic disease and curative surgical options are rarely (<25%) possible (28). Single-agent chemotherapy with streptozocin yielded tumour response rates of 36-42%, but these early studies can be criticised for using crude methods to interpret morphological responses (29). Other monotherapies, including chlorozotocin, doxorubicin, 5-fluorouracil (5-FU) and dacarbazine have been used, but criticised either for a high toxicity rate or a lack of objective response. Streptozocin, initially combined with 5-FU, and subsequently with doxorubicin yielded a 69% objective response rate and a median survival of 26 months, in a study by Moertel *et al* and this combination became the standard therapy (30). While no group has managed to achieve the same response rates as Moertel, objective responses of 36-55% have been established using streptozocin and doxorubicin, with the exception of two small retrospective studies where response rates of 6% were reported in both studies (31). However, in a more recent study by Delaunoid *et al*, 45 patients showed a 36% overall response rate using well-defined criteria for recruitment and evaluation (32), in addition, the 2- and 3-year overall survival rates were 50 and 24%, respectively. Such discrepancies are likely to be related to differences in overall study size and differences in the criteria used to measure response. The triple combination streptozocin, doxorubicin and 5-FU gave a 39% objective response, and more recently, streptozocin and liposomal doxorubicin a 40% response rate (33). This latter study was interesting in that it reported no cardio-toxicity (the prevalence of cardiomyopathy increases significantly when patients are given doses of doxorubicin >550 mg/m^2). The use of streptozocin requires careful monitoring of renal function. Other combinations used have included capecitabine and oxaliplatin with a 27% response rate and stabilization achieved in 45% of patients (34). Gemcitabine and oxaliplatin give a 40% objective response in a small number of patients (35). Temozolomide, an oral form of dacarbaxine, had recently gained favour in the treatment of pancreatic GEP-NETs. Dacarbaxine monotherapy (i.v. every 4 weeks) was previously shown to give 39% response rates (36), and the interesting results achieved by temozolomide (37) in central nervous system tumours prompted its use in GEP-NETs. Although the data surrounding temozolomide remain relatively preliminary, 8-70% response rates have been achieved either as monotherapy or in combination with thalidomide or capecitabine (38). Temozolomide has the advantage of being relatively well tolerated, being available as an oral therapy and has been reported to give impressive disease stabilization in heavily pre-treated patients. A direct randomized comparison of temozolomide alone or in combination with other therapies, or of temozolomide with either standard chemotherapy (streptozocin and doxorubicin) or targeted therapies (sunitinib or everolimus) would appear to be logical steps in testing this interesting molecule.

Midgut. Multiple molecules, used as either a single-agent or in combination strategies, have been tested to treat gastrointestinal and largely midgut NETs with disappointing objective response rates ranging from 0 to 40% and response durations

rarely exceeding 3 months (39). Again, a 5-FU and streptozocin combination initially gave a 33% response rate but later studies using the same combination were disappointing (40). More recent studies have failed to justify cytotoxic combinations in midgut GEP-NETs. A large phase II/III trial evaluated 176 patients randomized to streptozocin plus 5-FU or doxorubicin plus 5-FU (41). Patients crossed over to dacarbazine treatment after disease progression following first-line treatment. There were no differences in response rate (16 and 15.9%, respectively) and PFS was 5.3 and 4.5 months respectively in both arms. However, patients randomized to streptozocin plus 5-FU experienced a longer survival (24.3 months) than the patients randomized to doxorubicin plus 5-FU (15.7 months). The response rate of crossover dacarbazine treatment was 8.2%, with a median survival of 11.9 months. Recent trials examining oxaliplatin in combination with either gemcitabine or capcetabine report no response rates. Temozolomide has yielded modest response rates in treating advanced midgut GEP-NETs (9%) but this single agent achieved respectable stabilization (70%) in patients heavily pre-treated prior to temozolomide commencement. Overall, international recommendations have suggested abandoning the use of classical cytotoxics in the treatment of metastatic midgut tumours in favour of more suitable options when applicable (e.g., transarterial chemoembolization, peptide receptor radionucleotide therapy (PRRT), targeted agents, or enrolment in clinical trials) (42).

6. Targeted therapies in advanced GEP-NETs

Bevacizumab. Most well differentiated endocrine tumours are richly vascular and many express VEGF receptors (43). In a xenograft model of a human carcinoid, treatment with an anti-VEGF monoclonal antibody was found to inhibit tumour growth and metastasis (44). As the role of angiogenesis and hypoxic-related factors appears to be clearly related to tumour aggressiveness, strategies using agents which target angiogenesis have been developed. Bevacizumab with depot octreotide gave a partial response of 18% and a 77% disease stabilization in a recent phase II trial (45). In this trial, bevacizumab was also demonstrated to inhibit tumour blood flow at day 2 and week 18. Bevacizumab in combination with chemotherapy is also under examination. Preliminary results of a phase II trial combining bevacizumab, capecitabine plus oxaliplatin in 40 patients with advanced disease (20 pancreas, 5 small bowel and 15 unknown or other GEP-NETs) reported 7 partial responses (23%; 6 had pancreatic primaries) with a median PFS of 13.7 months (46). Another preliminary report from a phase II study examining bevacizumab and Folfox in non-pancreatic GEP-NETs showed 20% (1/5) partial responses and 80% (4/5) stabilizations and slightly poorer results for pancreatic GEP-NETs (partial responses 33% (2/6) and 66% (4/6) stabilizations (47).

Tyrosine kinase inhibitors. A number of small molecule tyrosine kinase inhibitors have been evaluated in advanced NETs. The most promising activity has been observed with sorafenib, pazopanib, or sunitinib, all of which have activity against VEGF receptor (VEGFR). The small molecule tyrosine kinase inhibitor sorafenib has activity against VEGFR-2 and platelet-derived growth factor receptor B (PDGFR-B), and was evaluated in 50 patients with carcinoid tumours and 43 patients with pancreatic NETs. In a preliminary analysis, responses were observed in 7% of the carcinoid patients and 11% of the patients with pancreatic NETs (48). Pazopanib, a tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, and c-kit, was evaluated in a prospective study of 51 patients with advanced NETs (29 with pancreatic NETs and 22 with carcinoid tumours) on stable doses of octreotide-LAR. Patients received pazopanib at a dose of 800 mg daily. The response rate among patients with pancreatic NETs was 17%; no patients with carcinoid experienced a radiographic response (by response evaluation criteria in solid tumours-RECIST) (49). Sunitinib works by blocking multiple molecular targets implicated in the growth, proliferation and metastatic spreading, of tumour cells acting via VEGF-R, PDGFR and other targets important to tumour growth, including KIT, FLT3 and RET (50). The first report of clinical activity for sunitinib in GEP-NETs was recently reported by Kulke *et al* (51). This was a phase II trial involving 107 patients with mixed GEP-NETs treated with sunitinib (carcinoid tumours, n=41; pancreatic NETs, n=66). Respective overall objective response rate in pancreatic and carcinoid GEP-NETs were 17% (11/66) and 2% (1/41); the corresponding disease stabilization rates for both tumour groups were 68% (45/66) and 83% (34/41), respectively. The median time to tumour progression was 7.7 months in pancreatic GEP-NETs patients and 10.2 months in carcinoid tumour patients. One-year survival rate was >80% in both groups of patients. The treatment was well tolerated. A recent phase III trial examining sunitinib as monotherapy vs. placebo in 340 planned patients was performed in well differentiated advanced and progressive pancreatic GEP-NETs. Prior systemic therapy had been administered to 66 and 72% of patients treated in the treatment vs. placebo arms, respectively. The study was terminated early at an unplanned interim analysis after enrolment of 171 patients and 81 PFS events. The median PFS (primary endpoint) was 11.4 months in the sunitinib arm vs. 5.5 months in the placebo arm (HR 0.418). However, due to the number of interim looks, the PFS difference did not reach statistical significance. Objective response rates for sunitinib was 9.3 vs. 0% for placebo and objective progression was almost double in the placebo arm (27.1 vs. 14.0%). These results were achieved at the expense of non-negligible toxicity for the active treatment arm (notably diarrhoea (59 vs. 38%), hand-foot syndrome (22.9 vs. 2.4%) and hypertension (26.5 vs. 4.9%) (52).

mTOR inhibitors. Mammalian target of rapamycin (mTOR) is a conserved serine-threonine kinase that regulates the cell cycle and metabolism in response to environmental factors. It mediates signalling transduction downstream of receptor tyrosine kinases and has been linked to pathways involved in the pathogenesis of GEP-NETs in several models. In addition, mTOR inhibition suppression was found to suppress NET growth (53). Yao *et al* conducted an initial phase II study using the mTOR inhibitor RAD001 (everolimus), at two does (5 or 10 mg/day) in association with octreotide LAR 30 mg every 28 days in a group of 30 patients with pancreatic GEP-NETs and 30 with non-pancreatic gastrointestinal GEP-NETs (54). The intent-to-treat response rate was 20% and per protocol, there were 13 patients with partial responses (PR; 22%), 42 with stabile disease (SD; 70%), and five patients with progressive disease (PD; 8%).

Overall median PFS was 60 weeks. Median overall survival had not been reached and 1-, 2- and 3-year survival rates were 83,81, and 78%, respectively. Mild aphthous ulceration occurred in 8% of patients and the grade 3/4 toxicities occurring in >10% of patients included hypophosphatemia (11%), fatigue (11%), and diarrhoea (11%). Importantly, anti-tumour activity was noted for patients with non-pancreatic gastrointestinal GEP-NETs: 5/30 (17%) confirmed partial responses, 24 SD (80%), and one PD (3%). In the pancreatic GEP-NETs group, there were 8/30 PR (27%), 18 SD (60%), and 4 PD (13%). Response was higher for the 10 mg RAD001 dose cohort (30 vs. 13% PR). These results paved the way for a large open-labelled phase II trial (Radiant 1), which examined, in a stratified manner, everolimus (RAD001) 10 mg/day and everolimus 10 mg/day plus octreotide depot (every 28 days) in patients with advanced pancreatic GEP-NETs with progression during or after chemotherapy. Synergy between RAD001 and octreotide had been previously suggested as octreotide may protect against a potential RAD001 resistance mechanism via inhibition of IGF pathways (55). Radiant I demonstrated a PR of 9.6% for everolimus and 4.4% for everolimus/octreotide therapy. The corresponding rates of disease stabilizations were 68 and 80% for the monotherapy and combined therapy groups, respectively; median PFS was 9.7 months for everolimus alone and 17.7 months for everolimus combined with octreotide. Thereafter two large randomized phase III trials examined the use of everolimus in the treatment of pancreatic and non-pancreatic NETs. Radiant III compared everolimus 10 mg/day alone to placebo and best supportive care in 410 pancreatic NET patients (56). The groups were well matched for disease extent and prior therapies before study enrolment. The primary endpoint, PFS, was significantly longer in the everolimus group (11.0 months vs. 4.6 months; HR 0.35). While confirmed responses were only 4.8% in the active arm (vs. 2.0% in placebo), overall disease control rates (complete or partial response and SD) was significantly higher in the everolimus arm (78 vs. 53%). Radiant II was a similar study in a more mixed group of patients with advanced NETs and carcinoid syndrome (n=429) where everolimus with octreotide was compared with placebo/octreotide combinations (57). The primary endpoint, PFS, almost achieved statistically significance (16.4 months vs. 11.3 months in everolimus vs. placebo groups; HR 0.77). Imbalances in the groups were noted as the everolimus/octreotide group had significantly more lung NET primaries (15 vs. 5%, P<0.05) and had received more systemic chemotherapy (35 vs. 26%, P<0.05) than the placebo/octreotide group (58).

7. Conclusions

Approximately two-thirds of malignant GEP-NETs are metastatic at discover. Surgery is possible in only a minority of patients, and therefore chemotherapy, with or without other strategies (e.g. local ablation), is frequently indicated in patients with symptomatic, bulky or progressive disease (59). For well-differentiated pancreatic GEP-NETs the reference association of streptozocin/doxorubicin (or 5-FU) yields objective responses in approximately 35-40% of patients but treatment is limited due to the potential toxicity. The approval of sunitinib in advanced progressive pancreatic GEP-NETs allows for a welcome alternative therapy and while responses rates are low, disease stabilizations appear impressive. Similarly, everolimus will almost certainly be approved for the same indication, allowing for a number of strategies to be employed in cases of advanced pancreatic GEP-NETs. Temozolomide appears to have impressive anti-tumour activity for pancreatic GEP-NETs and requires comparison with other established therapies. Published studies which evaluate chemotherapy for midgut and other gastrointestinal GEP-NETs are poor, outdated, disappointing, and cannot be recommended. In patients with low-volume and grade 1 tumours, somatostatin analogues are effective in preventing disease progression. The results of everolimus in combination with octreotide are formally awaited and may prove an alternative strategy. However, therapies such as chemoembolization or peptide receptor radionuclide therapy should be considered in gastrointestinal GEP-NETs. Little progress has been made for poorly differentiated GEP-NETs that respond to platinum/etoposide combined therapies but where disease control proves to be limited (60,61).

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Authors' contributions

PG designed the current review, wrote the manuscript, edited and analysed the data.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The author declares that they have no competing interests.

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