

Medical treatment for gastro-entero-pancreatic neuroendocrine tumours

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Abstract

Gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) represents a various family of rare tumours. Surgery is the first choice in GEP-NENs patients with localized disease whilst in the metastatic setting many other treatment options are available. Somatostatin analogues are indicated for symptoms control in functioning tumours. Furthermore they may be effective to inhibit tumour progression. GEP-NENs pathogenesis has been extensively studied in the last years therefore several driver mutations pathway genes have been identified as crucial factors in their tumourigenesis. GEP-NENs can over-express vascular endothelial growth factor (VEGF), basic-fibroblastic growth factor, transforming growth factor (TGF- α and - β), platelet derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1) and their receptors PDGF receptor, IGF-1 receptor, epidermal growth factor receptor, VEGF receptor, and c-kit (stem cell factor receptor) that can be considered as potential targets. The availability of new targeted agents, such as everolimus and sunitinib that are effective in advanced and metastatic pancreatic neuroendocrine tumours, has provided new treatment opportunities. Many trials combing new drugs are ongoing.

Key words: Neuroendocrine neoplasms of the gastro-entero-pancreatic system; Chemotherapy; Targeted agents; Somatostatin analogues; Everolimus; Sunitinib

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Core tip: In this review, recent evidences in the biology and pathology of neuroendocrine neoplasms of the gastro-entero-pancreatic system were analysed, focusing on new biological perspectives of medical treatment. The

evidence-based data of new-targeted drugs and the new molecular knowledge are summarized looking at the basis for future studies.

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INTRODUCTION

Neuroendocrine neoplasms of the gastro-entero-pancreatic system (GEP-NENs) include a heterogeneous group of disease emerging from neuroendocrine cells of gastro-intestinal tract and pancreatic islets^[1]. Nevertheless, despite their morphologic, clinical and prognostic heterogeneity, GEP-NENs are often considered as a single entity^[2].

Although still considered a rare disease, SEER data showed an increasing incidence in the last three decades up to 3.65/100000 per years^[3]. This may be due to a remarkable improvement of diagnostic technique as well as a real change in population demography^[4]. GEP-NENs are more frequently detected in adult population^[5] and in about 50% of cases nodal (25%) or distant (25%) metastases are already existing from the beginning^[3,6]. On the basis of their morphologic features and proliferation index, NENs are currently stratified in two groups, according to WHO 2010 classification criteria^[7]: Neuroendocrine carcinomas, G3 tumours with ki67 proliferation index > 20%, and neuroendocrine tumours (NETs), including G1 (ki67 < 3%) and G2 (ki67 between 3% and 20%) neoplasms. Neuroendocrine carcinomas represent a separate cluster in the family of NENs, with specific biological features and a more aggressive behavior, so chemotherapy is currently considered the standard of care in this specific set^[8,9]. Conversely well and moderately-differentiated NENs do not represent a single entity and their pathogenesis has become clearer in recent years. In fact many driver mutations pathway genes have been identified as crucial factors in their tumourigenesis. Therefore altered pathways represent as a profitable therapeutic choice in neoplastic disease and also in NENs^[10-13].

Despite extensive and remarkable medical exertions, therapeutic choices are still unsatisfactory, mainly due to the lack of a broad knowledge of biological mechanisms and predictive factors. This review aims to summarize the present knowledge about chemotherapy and the pathways involved in sporadic well and moderately differentiated GEP-NETs, highlighting available evidences and new biological perspectives on biological and targeted therapies.

CHEMOTHERAPY

Although most of the studies were conducted on a heterogeneous population and the relationship between response rate (RR) and proliferation index value is often not clearly defined, GEP-NENs, therapy should include cytotoxic agents, especially in symptomatic subjects, progressive disease, moderated differentiation and more aggressive features. Chemotherapy should also be evaluated when the aim is to obtain a response in case of bulky lesions. However the best sequence for chemotherapy still remains uncertain^[14-18].

The most common used chemotherapy schemes include alkylating agents [streptozotocin (STZ), dacarbazine, temozolomide], antimetabolites [5-fluorouracil (5-FU), capecitabine] and platinum derivatives.

Temozolomide combined with 5-FU^[19] or capecitabine^[20] can represent the regimen of choice in G1 and G2 advanced P-NENs. Retrospective data showed a RR of 70% and progression-free survival (PFS) of 18 mo for temozolomide and capecitabine combination^[20].

Furthermore the association of STZ and 5-FU is frequently evaluated as a first-line therapy for advanced P-NENs with RRs between 6% to 40%, with the benefit in PFS ranging between 5 and 20 mo and with a median overall survival of 16-24 mo^[19].

Then, oxaliplatin in combination with capecitabine could also be considered for different setting of G1-G2 GEP-NETs^[15]. None of small retrospective studies or case reports conducted with other chemotherapy regimens have demonstrated sufficient efficacy in GEP-NETs.

SOMATOSTATIN

Many studies have shown the importance of somatostatin in the regulation of NENs' physiological functions. Currently, a cluster of five distinct somatostatin receptors (SSTRs) has been characterized in humans (SSTR1-SSTR5)^[21,22].

The presence of SSTRs has been demonstrated in over 80% of well-differentiated GEP-NENs, with a clear predominance of SSTR2 both in GI-NENs (90%) and P-NETs (80%)^[23,24].

Among the different SSTR subtypes, SSTR2 is usually the most prevalent in NENs, after that SSTR1 and SSTR5, whilst SSTR3 is less commonly expressed and SSTR4 almost absent^[25-27].

In general, tumour dedifferentiation is usually associated with a reduction of receptor density and changes in receptor subtype profile; thus, the presence of SSTRs might be also useful as a tumour specific predictor of prognosis.

Furthermore, the presence of SSTR5 seems to correlate with a major risk of angioinvasion and distant metastasis^[28]; instead, the loss expression of SSTR2 could be highly associated with the dysregulation of tumour proliferation, consequently promoting tumour growth^[29]. The lack of SSTR2

induces the generation of new membrane dimers, with development of different receptors, characterized by new function^[29-36]. It remains unclear if only numeric reduction of SSTRs or also their down-regulation are linked with tumour dedifferentiation^[37]. In pancreatic gastrinomas, glucagonomas and VIPomas, SSTRs are high expressed (80%-100% of patients). However, SSTRs seem to be expressed in 50%-70% of insulinomas, especially SSTR5 mRNA expression was demonstrated to be positively correlated with histopathological features of tumour aggressiveness in primary insulinomas^[38].

Therefore, in P-NENs subtypes, which express less SSTR, short synthetic analogues of somatostatin (SSAs) show a reduced activity in symptoms' control with a worsen hypoglycaemia^[39,40]. This high and heterogeneous expression does not show any relevant correlation between the subtype(s) expressed and the primary tumour origin, or a specific hormone secretion^[41-43].

The intracellular pathways activated by SSTRs appear different in several types of tumour cells and depend on the specific SSTR distribution pattern, signalling elements, as well as to receptor desensitization, internalization, and cross talk^[44,45].

The activation of G-proteins regulates the different critical enzymatic proteins such as adenylyl cyclase and protein kinase A, phospho-tyrosine phosphatases (PTPs) and mitogen activated kinases (MAPKs)^[22,46,47].

In particular SSTR1 induces MAPK pathway activations, SSTR2 improves SHP1 and epidermal growth factor receptor (EGFR) work, up-regulate p21 and Rb reducing MAPK switching on and blocking cellular proliferation. SSTR3 activates p53 and Bax inducing apoptosis, besides it blocks vascular EGFR (VEGFR). SSTR5 induce the activations of PTPs. Globally, these mechanisms leads to an inhibition of cellular proliferation and hormones secretion. Conversely, SSTR4 promotes cell mitosis up-regulating MAPK/ERK1/2 pathway^[21,48].

Since the 80s', several SSAs including octreotide, lanreotide, vapreotide, seglitide and pasireotide, were studied. In contrast to the endogenous somatostatin, these peptides have a more durable half-life (1.5-2 h vs 1-2 min) and activity, as they have a greater resistance to peptidase^[49].

Furthermore, compared to native somatostatin, they have diverse affinity for the aforementioned receptor subtypes^[25,37,50]. In particular the natural ligands of SSTR1-5 can bind all SSTRs with high affinity. Conversely different SSAs, in the same cell type, may elicit differential effects, due to the activation of different subsets of intracellular mediators^[45,51,52].

The analogues octreotide, lanreotide, vapreotide and seglitide exhibit elevated affinity for SSTR2 and lower for SSTR3 and SSTR5. Multi-SSTR-targeted analogue SOM230 (pasireotide) shows higher binding capacity towards SSTR1 and activates also SSTR 2, 3 and 5^[50,53].

The various SSTR binding show a different affinity with their own ligands, which is responsible for the distinct biological and clinical activity^[37]. Imam *et al*^[54] and Eriksson *et al*^[55] demonstrated a pro-apoptotic role of

SSAs. In fact they analysed tumor samples of GEP-NENs patients, who received high doses of SSAs^[54,55], finding increased apoptosis processes. The antiproliferative effect of SSAs is mediated by direct and indirect mechanisms. The inhibition of SSTRs, if expressed on tumour cells' membrane, operates directly on cell proliferation, stimulating antimitotic and apoptotic activities. SSAs induce cell growth inhibition also with indirect activities, such as angiogenesis inhibition, modulation of immune system and growth factors' block.

The indirect antiproliferative efficacy of SSAs does not require SSTR tumour expression and is shown by an antiangiogenic or immunomodulation mechanism, mediated by stimulation of the production of natural-killer cells^[56-58]. The antiproliferative activity of SSAs has been shown through various experimental models^[59-64]. The indication of using SSAs as fundamental therapy in NETs derives mainly from two studies: PROMID and CLARINET trials^[65,66]. The PROMID study showed a significant benefit with octreotide LAR (long-acting release) therapy in 85 subjects affected by advanced midgut NENs.

This study demonstrated an advantage in time to progression (TTP). In fact in patients treated with octreotide LAR a mTTP of 14.3 mo was observed, whilst patients in the control arm, receiving placebo, reported a mTTP of 6 mo. Sixty-four percent of subjects in the experimental arm showed stable disease (SD), which was observed only in 37.2% of subjects assuming placebo. Furthermore, patients treated with octreotide LAR experienced a 67% risk reduction of tumour progression compared with patients receiving placebo. The benefit of octreotide LAR was independent either of chromogranin level or hormone secretion.

The study did not show significant differences in OS, presumably due to the few deaths' percentage in both treatment arms. Furthermore the failure of the demonstration of an impact of octreotide in survival could be also done to the high rate of cross-over^[67].

Based on PROMID results, octreotide LAR has been approved as treatment of recurrent and advanced neuroendocrine tumors' patients, irrespective of the site of primary tumour, functional status and symptoms' presence. Lanreotide is another SSA with a similar *in vitro* hormone release inhibitory profile to octreotide^[68].

Recently, the CLARINET trial focused on 204 subjects suffering of nonfunctioning GEP-NENs who were randomized to receive either depot lanreotide, 120 mg every 4 wk for 96 wk, or placebo. The study demonstrated an improvement in PFS for patients treated with lanreotide (mPFS not reached in lanreotide arm; mPFS of 18 mo in placebo arm). This benefit was confirmed both in patients with P-NENs and midgut NENs.

Pasireotide, a new SSA, is characterized by an elevated binding affinity to four of the five SSTR sub-types^[69]. Hence, due to its broad binding profile, pasireotide may represent an effective therapeutic opportunity in tumours refractory to octreotide or lanreotide^[70]. However, its role in GEP-NETs still remains to be defined. In a phase III study pasireotide did not improve the control of flushing

Table 1 Ongoing phase III trials in gastro-entero-pancreatic neuroendocrine tumours

ClinicalTrials.gov Identifier	Investigated drug	Target	Type of enrolled pts
NCT00171873	Octreotide LAR 30 mg	SSTR	Locally inoperable or metastatic well differentiated NETs of the midgut Naïve pts
NCT01524783	Everolimus plus BSC <i>vs</i> PBO plus BSC	mTOR	Unresectable or metastatic G1 or G2 neuroendocrine tumours of GI or lung Treatment-naïve pts and pre-treated pts (all available treatment options are allowed) with PD
NCT00842348	Lanreotide autogel 120 mg	SSTR	Non-functioning GEP-NETs
NCT00690430	Pasireotide LAR 60 mg <i>vs</i> Octreotide LAR 40 mg	SSTR	Metastatic carcinoid tumours
NCT00774930	Somatuline depot (lanreotide) <i>vs</i> PCB	SSTR	Pts with disease-related symptoms inadequately controlled by somatostatin analogues Carcinoid tumours with liver metastasis
NCT00092287	Lanreotide autogel <i>vs</i> Sandostatin LAR	SSTR	Treatment-naïve pts and pts pre-treated with and responsive to somatostatin analogues Carcinoid tumours localized in lung, stomach or midgut
NCT00263659	Telotristat etiprate (LX1606) <i>vs</i> PBO	TPH	Well-differentiated metastatic NETs with carcinoid syndrome Treatment-naïve pts
NCT01677910	Telotristat etiprate (LX1606) <i>vs</i> PBO	TPH	Well-differentiated metastatic NETs with carcinoid syndrome Pts with disease-related symptoms inadequately controlled by somatostatin analogues

GEP-NETs: Gastro-entero-pancreatic neuroendocrine tumours; LAR: Long acting release; SSTR: Somatostatin receptor; mTOR: Mammalian target of rapamycin; BSC: Best supportive care; PBO: Placebo; PD: Programmed death; TPH: Tryptophan hydroxylase; pts: Patients.

or diarrhea in patients affected by refractory carcinoid syndrome^[71] (Table 1). The antiproliferative effects are being tested in several clinical studies^[72,73]. Telotristat etiprate (LX1606) is an oral serotonin synthesis inhibitor used in patients with diarrhoea related to carcinoid syndrome^[74].

A recent randomized prospective single-arm study has been conducted in patients with carcinoid tumour and diarrhoea (≥ 4 bowel movements/day) inadequately controlled by octreotide. Among patients treated with telotristat etiprate, 28% experienced a $\geq 30\%$ reduction in bowel movements frequency for more than 2 wk and 56% had a biochemical response. These results suggest a potential activity of telotristat etiprate in controlling carcinoid syndrome and diarrhoea. Pavel *et al*^[75] made a prospective exploratory dose escalating 12-wk open label multicentre study of telotristat etiprate in metastatic well-differentiated NETs with ≥ 4 -bowel movements/day. Whole patients experienced reductions in bowel movements, 74.2% mean reduction in metabolites of serotonin and 75% of patients reported adequate relief of GI symptoms (Table 1).

MAMMALIAN TARGET OF RAPAMYCIN PROTEIN KINASE B, PHOSPHOINOSITIDE 3-KINASE AND PHOSPHATASE AND TENSIN HOMOLOG PATHWAY

A considerable number of intracellular pathways seem to conditionate tumorigenesis and neoplastic spread in NENs, as receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) transduction mechanisms. Their action seems to be modulated by Ras/Raf, MAPK, phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) and JNK

increasing cells' growth and number. The AKT family of serine/threonine kinases is an important mediator of PI3K signaling, promoting the principal cellular functions^[76]. Akt isoforms seem to be an eminent target for GEP-NENs therapy^[77]. PI3K/AKT/mTOR pathway is especially activated among P-NENs^[78] and their somatic mutations are detected among a minority of P-NETs^[79]. Although discrete mutations in the aforementioned pathway are rarely found in GEP-NENs, overexpression of mTOR and/or its downstream targets is being individuated in a high frequency of cases and it is correlated with higher proliferative activity and adverse clinical outcomes^[80,81]. mTOR is composed by two complexes working together guarantying many cells' activities^[82-91]. The importance of mTOR inhibitors results from the aforementioned considerations^[92,93]. RADIANT-1 (phase II study) represents the first trial demonstrating everolimus utility in GEP-NETs^[94]. The trial compared everolimus alone *vs* everolimus plus octreotide in 160 patients. Regarding combined therapy arm the median PFS was 16.7 mo with a quite well tolerance.

In RADIANT-2 (phase III trial) subjects affected by symptomatic well-differentiated NETs received everolimus plus octreotide *vs* octreotide alone. A lack of significant benefit in PFS was showed in the combination arm. The most common grade 3/4 side effects in the everolimus arm were stomatitis (6.5%), diarrhea (6%), infections (5.1%), and hyperglycemia (5.1%)^[95]. RADIANT-3 (phase III trial) contemplated everolimus *vs* placebo^[96]. The study recruited only G1-G2 P-NETs subjects. Everolimus arm was associated with a better PFS although a low ORR. Therefore everolimus was approved in the management of advanced P-NETs.

RADIANT-4 (ongoing phase III trial) investigates role of everolimus in gastrointestinal/pulmonary neuroendocrine tumors. It may lead to a better definition of the role of

Table 2 Ongoing phase II trials in gastro-entero-pancreatic neuroendocrine tumours

ClinicalTrials.gov Identifier	Investigated drug	Target	Type of enrolled pts
NCT01841736	Pazopanib	VEGFR PDGFR FGFR c-kit	Progressive carcinoid tumours
NCT02399215	Nintedanib	VEGFR FGFR PDGFR	Carcinoid tumour Metastatic carcinoid tumour Neuroendocrine neoplasm
NCT01994213	Famitinib	c-kit PDGFR VEGFR Flt	Gastroenteropancreatic neuroendocrine tumour
NCT01121939	Bevacizumab plus pertuzumab plus sandostatin LAR	VEGF HER2	Advanced neuroendocrine cancers
NCT02259725	Regorafenib	c-RAF BRAF VEGFR PDGFRa FGFR-1 c-kit RET Flt-3	Gastrinoma Glucagonoma Insulinoma Metastatic gastrointestinal carcinoid tumour Pancreatic polypeptide tumour Pulmonary carcinoid tumour Recurrent gastrointestinal carcinoid tumour Recurrent Islet cell carcinoma Somatostatinoma
NCT01784861	X-82 plus everolimus	mTOR	Pancreatic neuroendocrine tumours
NCT01508104	BEZ235 plus everolimus	PI3K	Advanced cancers of different types
NCT00781911	Cixutumumab	IGF-1R	Neuroendocrine tumours

VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet derived growth factor receptor; FGFR: Fibroblast growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; IGF-1R: Insulin-like growth factor-1 receptor; pts: Patients.

everolimus in patients with carcinoid tumours. Finally, other targeted therapies are being studied in NETs (Table 1). Furthermore temsirolimus, another mTOR inhibitor, was evaluated in NETs^[97]. However, the results were not considered clinically relevant and further studies with this agent in NETs won't be performed.

Another fundamental target implicated is PTEN (phosphatase and tensin homologue). Loss of PTEN is commonly individualized in a several human cancers^[98] and it is related to the presence of metastases and therapy resistance towards mTOR inhibition^[99-103]. PTEN is localized in the nucleus. Its activation through internalization leads to a reduction of Act^[104-106]. PTEN is frequently mutated in P-NETs and a low expression of PTEN correlates with high grading^[107].

PI3K pathway represents a hot point in NETs proliferation and some studies evaluating its inhibition are ongoing. BEZ235 is a PI3K inhibitor studied associated with everolimus (phase II study) (Table 2). Then a phase I study is on-going using BYL179 in combination with everolimus and exemestane in P-NETs.

INSULIN GROWTH FACTOR-1

Insulin growth factor 1 (IGF-1) represents a fundamental factor in tumour expansion, so its inhibition may reduce tumour proliferation. NETs have demonstrated to secrete

a significant quantity of IGF-1, then its receptor (IGF-1R) shows a key role in GEP-NETs tumorigenesis^[108,109].

Furthermore, many evidences have related a major IGF-1R expression with the presence of functioning and symptomatic NETs^[109-118]. Cixutumumab (CIX), a monoclonal antibody competitively binding IGF-1R and then causing its degradation, is currently being evaluated in an on-going trial in association with octreotide depot (Table 2). The usefulness of CIX has already been demonstrated in combination with many other therapeutic options^[119].

VEGF

Angiogenesis displays a crucial role for tumour expansion and distant spread and it's mediated by VEGF and its receptors (VEGFRs). Four VEGF forms were identified: VEGF-A, VEGF-B, VEGF-C and VEGF-D, with a different affinity to their three own receptors^[120-129]. Octreotide showed an inhibition of angiogenesis probably mediated by an interaction with VEGF pathway^[130]. The tyrosine kinase inhibitor (TKI) sunitinib^[131] has been demonstrated a valid targeted therapy option in NENs.

A phase II trial evaluated the efficacy of sunitinib in GEP-NETs demonstrating a significant antitumour activity in P-NETs, while among patients with carcinoid tumours OR were only 2.4%; the treatment was average well

tolerated with especially gastrointestinal toxicities^[132].

As a consequence of these results, a phase III trial evaluated sunitinib vs placebo in 171 low- and intermediate-grade advanced P-NETS^[133]. In the experimental arm was demonstrated an improvement of PFS although the RRs associated with the drug were only 9.3%. The benefit was independent of previous treatments and concomitant administration of SSAs. Considering the importance of VEGF in pathogenesis of NENs, bevacizumab, an antibody directed against VEGF^[134], has been used either alone or in combination with other drugs with favourable results^[135].

CYTOTOXIC T-LYMPHOCYTE ANTIGEN-4 AND PROGRAMMED DEATH-1

Recently, immunotherapy was demonstrated to be an important treatment option in various cancers. In fact several new immune-target drugs, directed towards specific immune checkpoints, showed an important antitumoral effect.

The first developed immune agents were directed against mediator of immunity inhibition, as cytotoxic t-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1). These mediators are both membrane glycoprotein, which are mainly expressed in activated T-lymphocyte.

CTLA-4, known also as CD152, owns an elevated kinship with CD28 and plays a crucial role regulating immunity's homeostasis, through the switching-off of T-lymphocyte activation. Its expression seems to be mayor stimulated in switched-on effector T-lymphocytes (Teff cells)^[136]. CTLA-4 is constitutive and represented in regulatory T lymphocytes (Treg)^[137]. As aforementioned said, it joints CD28, thanks to theirs high affinity, to costimulatory proteins (CD80, CD86) represented in antigen-presenting cells (APC).

Several humanized monoclonal antibodies directed vs CTLA-4, were studied, such as ipilimumab and tremelimumab. The programmed cell death protein-1, PD-1, a membrane protein, acts inhibiting a large group of molecules owing to CD28 family of T-lymphocytes regulators. PD-1 is most represented on surface membrane of activated monocytes, T lymphocytes, and B lymphocytes. PD-1 have different ligands, the most known are PD-L1^[138] and PD-L2^[139].

PD-L1, a transmembrane protein notably presents in macrophages, in T-ymphocytes, B lymphocytes and dendritic cells (DCs), its concentration increases since cellular activating processes. PD-L1 may be presented also in some tissues not involved in immune system. The principal function of PD-1 seems to be reducing autoimmunity and switching off T-lymphocyte activities involved in inflammatory response to infection^[140-142].

In conclusion the linkage between PD-1, mainly expressed in activated T-lymphocytes and PD-L1, principally expressed in tissue DCs, induce a switching-off of T-lymphocytes activation and a blockage of their effector activity^[143]. Identifying a selected group of NENs' patients

that could benefit from immunotherapies is not still possible because no predictive biomarkers to immune drugs have been found. Further studies are needed to evaluate the exact expression of aforementioned target immune proteins (PD-1, PD-L1/L2) in the various NENs.

EGF AND TRANSFORMING GROWTH FACTOR ALPHA

EGF and transforming growth factor alpha (TGF- α) are polypeptides that bind the EGFRs regulating cellular responses to growth signals through activating signal transduction pathways (RAS-RAF-MAPK). From a biological point of view, EGF is a mitogen factor regulating growth, proliferation and differentiation of numerous cell types; abnormalities in EGF-signalling pathways have been related to tumour growth and progression^[144].

The EGFR belongs to the HER receptor family. Gastrointestinal (GI) and pancreatic NETs express and activate EGFRs^[145]. Papouchado *et al*^[146] demonstrated a most elevated presence of EGFR (> 91%) in GI-NENs, (especially in rectal NETs), whilst in P-NENs its expression was lower (< 25%).

Srivastava *et al*^[147] showed instead an elevated presence of EGFR and TGF- α , in P-NENs. Sixty-three per cent of neoplasms in fact showed positivity for TGF- α and 65% for EGFR. However the study did not demonstrate an association with measure, functional status, ability to secrete hormones, or biologic behaviour^[147].

TGF- α is expressed in approximately 70%-100% of NETs depending on the technique used (immunohistochemistry or northern blot analysis)^[148-150] and is commonly over-expressed in larger rectal NETs with a high Ki-67 index^[150]. TGF- α binds with high affinity to the EGFR extracellular domain. Cytoplasmic substrates phosphorylation occurs and initiates a signalling cascade (RAS/RAF/MAPK-ERK) that drives pro-proliferative gene expression, cytoskeletal rearrangement, and increased cell proliferation^[144].

Gefitinib is a targeted agent that selectively inhibits receptor tyrosine kinases, including EGFR. A phase II trial enrolling subjects affected by advanced NENs, gefitinib exhibited somewhat promising initial results. At 6 mo, 61% of patients affected by carcinoid tumours and 31% affected by P-NEN were progression-free; however, objective responses for each group were low, 5% and 9.6%, respectively^[151].

BASIC FIBROBLASTIC GROWTH FACTOR

The basic fibroblastic growth factor (bFGF) is involved in both physiological and pathological processes by interaction with determined receptors localized in cellular membrane^[152,153].

Because overexpression of bFGF and/or its receptors is frequently detected in tumours, the development of antagonists to bFGF and its receptors has been studied as a potential strategy for cancer therapy^[154-156].

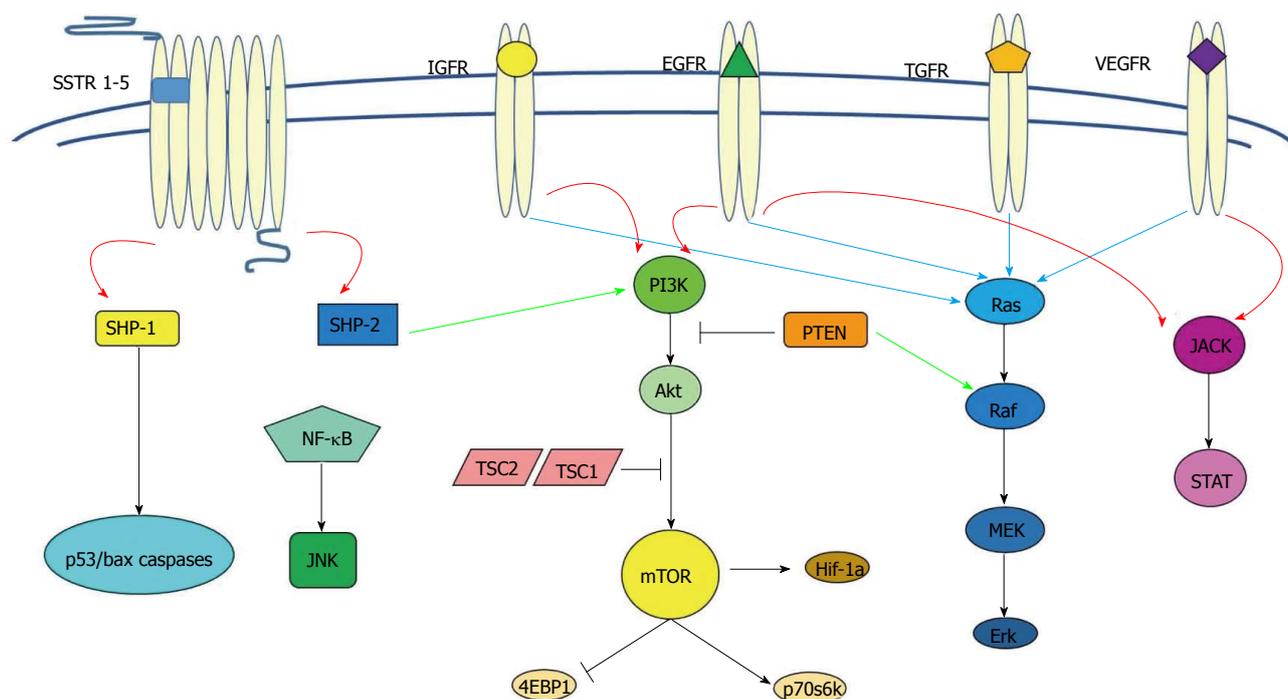


Figure 1 Illustration of principal pathways involved in cellular differentiation, proliferation, survival and apoptosis: Somatostatin receptors, mammalian target of rapamycin protein kinase B, phosphoinositide 3-kinase and phosphatase and tensin homolog, insulin-like growth factor 1 receptor, vascular endothelial growth factor receptor, epidermal growth factor receptor, transforming growth factor receptor, fibroblast growth factors. SSTRs: Somatostatin receptors; mTOR: Mammalian target of rapamycin; Akt: Protein kinase B; PI3K: Phosphoinositide 3-kinase; PTEN: Phosphatase and tensin homolog; IGFR: Insulin-like growth factor receptor; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; TGFR: Transforming growth factor receptor.

Almost five isoform of transmembrane FGF receptors (FGFR), able to dimerize, are well known. The first four subtypes are characterized by a tyrosine kinase activity^[157]. Chaudhry *et al.*^[158] searched for mRNA expression of 6 different transmembrane receptors (FGFR, EGFR, IGF-1R, TGF-betaR1 and betaR2), and the presence of SSTRs in determinate subtypes of GEP-NENs tissues (gastrinoma, insulinoma, tumours with carcinoid syndrome, not-functioning neoplasms) using reverse transcriptase-polymerase chain reaction. Among the four tumour subtypes, expression frequencies of the receptors aforementioned varied significantly^[158]. Taken together, these studies have accounted for high growth factor abundance in GEP-NENs. Considering these results GEP-NENs seems to have an elevated growth factors concentration.

C-KIT/ PLATELET DERIVED GROWTH FACTOR

The c-kit receptor, also referred to CD117 or platelet derived growth factor receptor (PDGFR) is a type I transmembrane glycoprotein. It is usually included in the family of tyrosine kinase receptor (RTK)^[159].

In tumor cells, PDGF promotes proliferation and neoplastic spread^[160-163]. Various subtypes of c-kit receptor have been already identified^[164] but their ligand still remains stem cell factor (SCF), a hematopoietic cytokine involved in cell survival, proliferation and differentiation^[165].

Few pre-clinical studies performed of GEP-NETs have shown a variable expression of c-kit, with ranges from 0% to 38%, and PDGFR α in carcinoids^[166], with a particularly high expression in gastrinomas (up to 100% of c-kit expression)^[167].

MULTI-TARGETED AGENTS

Famitinib is an oral tyrosine-inhibitor agent targeting at c-kit, PDGFR, VEGFR2, VEGFR3, Flt1 and Flt3. Its efficacy in GEP-NETs is currently being evaluated (Table 2).

Regorafenib is a novel multi-kinase inhibitor (c-RAF; BRAF, VEGFR-1, 2, 3; PDGFR α , FGFR-1; c-kit; RET; Flt-3) belonging to the group of biaryl urea chemicals^[168-170]. Pazopanib is an oral inhibitor of several specific cellular pathways involved in neoplastic growth and dissemination^[171]. Its efficacy in NENs was demonstrated in a phase II clinical trial combining pazopanib and SSA achieving a 17% RR in G1 P-NETs^[172]. Data related to ongoing trials with pazopanib and with regorafenib in NETs are summarized in Table 2.

CONCLUSION

In GEP-NETs tumourigenesis and progression are often involved SSTRs, mTOR/Akt/PI3K and PTEN, IGF-1, VEGF, EGF, TGF, FGF and c-kit/PDGFR and its corresponding receptors^[145,148,149,173-177] (Figure 1). The recent availability

of novel drugs has provided new treatment opportunities and holds promise given the expression in GEP-NENs of this variety of targets^[33,178,179].

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