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EDITORIAL

Treatment of gastrointestinal neuroendocrine tumors with inhibitors of growth factor receptors and their signaling pathways: Recent advances and future perspectives

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Abstract

The limited efficacy of conventional cytotoxic treatment regimes for advanced gastrointestinal neuroendocrine cancers emphasizes the need for novel and more effective medical treatment options. Recent findings on the specific biological features of this family of neoplasms has led to the development of new targeted therapies, which take into account the high vascularization and abundant expression of specific growth factors and cognate tyrosine kinase receptors. This review will briefly summarize the status and future perspectives of antiangiogenic, mTOR- or growth factor receptor-based pharmacological approaches for the innovative treatment of gastrointestinal neuroendocrine tumors. In view of the multitude of novel targeted approaches, the rationale for innovative combination therapies, i.e. combining growth factor (receptor)-targeting agents with chemo- or biotherapeutics or with other novel anticancer drugs such as HDAC or proteasome inhibitors will be taken into account.

Key words: Growth factor receptor; Neuroendocrine gastrointestinal tumor; Small molecule inhibitor; Monoclonal antibody; Multi kinase inhibition

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INTRODUCTION

Neuroendocrine tumors form a heterogeneous group of malignancies that do not only include gastrointestinal neuroendocrine tumors but also neoplasias such as pheochromocytoma, pituitary tumors, medullary thyroid cancer, and even undifferentiated (small cell) neuroendocrine cancer. Gastroenteropancreatic neuroendocrine tumors (GEP NET) are usually classified according to localization of the primary, grade of differentiation and functionality. The former traditional classification distinguished between pancreatic neuroendocrine tumors and carcinoid tumors[1]. Both tumor types often display well-differentiated histologic features, and often preserve the ability to release excessive amounts of biogenic amines and/or neuropeptides thereby causing characteristic hypersecretion syndromes. The resulting, often bizarre clinical symptoms are generally well controlled by somatostatin analogs or interferon-α[2,3]. However, tumor growth and spread of GEP NETs are not always well controlled by either biotherapy or chemotherapy. Thus, therapeutic options to inhibit growth and spread of gastrointestinal neuroendocrine tumors are still unsatisfactory.

Significant advances in our knowledge of the particular biology of GEP NETs made over the past decades shows that GEP NETs represent a tumor entity with an extraordinary high vascularization along with an abundant production and secretion of growth factors such as VEGF, EGF, IGF, PDGF, HGF, FGF or TGF-α. Expression and signaling of growth factors and their cognate receptors in GEP NETs has been studied quite extensively[4-10], and paved the way for new and molecular targeted strategies for GEP NET treatment. Among the most promising new therapeutic approaches is the inhibition of synthesis and/or secretion, as well as receptor binding of angiogenic

growth factors such as vascular endothelial growth factor (VEGF). These antiangiogenic approaches are mostly based on the use of specific monoclonal antibodies or tyrosine kinase inhibitors to attenuate tumor microvessel formation and hence the vital supply of the tumor with nutrients and oxygen[11,12]. Furthermore, dysregulation and/or overexpression of other oncogenic growth factor receptors in GEP NETs, such as the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor-1 (IGF-1R), or the platelet-derived growth factor receptor (mainly PDGFR-β) offer additional targets for future chemotherapeutic intervention[13,14]. These growth factor receptor-based strategies mainly target the receptors' intrinsic tyrosine kinase activity with small molecule inhibitors or ligand-receptor interactions with monoclonal antibodies. The underlying rationale for this treatment strategy is to specifically interrupt the downstream mitogenic and antiapoptotic signaling cascades that are triggered by ligand-activation of a specific growth factor receptor, events that have been shown to play a crucial role in the expansion and spread of the tumors.

Besides therapeutically targeting growth factor receptors, a third promising approach is the direct inhibition of receptor-mediated downstream signaling pathways such as the phosphatidyl-inositol-3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway or the Ras/Raf-mitogen-activated kinase (MAPK) pathway[15,16]. There is increasing evidence that specific inhibition of several key components of these pathways, such as mTOR and Raf, is thought to exert enhanced antineoplastic potency as compared to the single inhibition of just one pathway or pathway-activating receptor. Thus, the abrogation of single growth factor receptor activities are found to be counter-balanced by compensatory signaling and transactivation of other growth factor receptors[17-20].

This review will provide a perspective overview of selected agents, which are currently in development, consideration or testing for such targeted treatment approaches for GEP NET (Table 1). Moreover, promising approaches, which have not yet been evaluated in GEP NET, but warrant future evaluation, will be discussed.

ANTIANGIOGENIC TREATMENT STRATEGIES

Angiogenesis plays a central role in tumor growth and progression, and its implication has been extensively investigated and described in the literature for various cancers[21,22]. In the early 1970s, Folkman was the first to develop the concept of angiogenesis-dependent tumor growth and postulated that the specific blocking of blood flow to the tumor should be a promising strategy for cancer treatment[23].

Among the angiogenic factors/receptors described so far, the vascular endothelial growth factor (VEGF) and VEGF receptor family including the secreted glycoproteins VEGF-A (synonym: VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, the placental growth factors (PlGF-1, -2), and their cognate receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk/KDR) play major roles (not only in physiological) but also in pathological angiogenesis. VEGF that binds to both VEGFR-1 and -2 is the key regulator of the development of the vascular system and is commonly overexpressed in a variety of solid tumors[24]. Hypervascularized GEP NETs, have also been demonstrated to (over-)express VEGF and its cognate receptors (VEGFR-1, -2) in the tumor and its surrounding vasculature[25-28]. In addition, elevated levels of circulating VEGF are correlated with the progression of GEP NETs[29]. In this line, a recent study confirmed the particular role of VEGF for the prognosis and progression of GEP NET by showing that elevated expression of VEGF correlated with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors[30].

Based on the particular significance of VEGF and its receptors (VEGFR-1, -2) in GEP NETs and because of VEGF's action on endothelial cell activation for new tumor vessel formation, the VEGF/VEGFR system has been an extensively studied target for the treatment of GEP NET.

ANTIBODY-BASED ANTIANGIOGENIC THERAPY

Anti-VEGF treatment

Bevacizumab is a humanized murine monoclonal anti-VEGF antibody, which has entered the clinic for antiangiogenic treatment of cancer. Standard cytostatic treatment plus bevacizumab significantly increased survival in metastatic colorectal cancer as compared to standard treatment alone in a phase Ⅲ clinical trial[31], a finding that led to the approval of bevacizumab for treatment of colorectal cancer in 2005. Comparable results were obtained in a recent phase Ⅲ clinical trial with bevacizumab for treatment of non-small cell lung cancer (NSCLC). This study was interrupted before finalization because of the obvious survival advantage of patients in the bevacizumab arm[32].

The first clinical trials with bevacizumab for treatment of GEP NET were reported 3 years ago[33]. In a randomized Phase Ⅱ trial, the effect of monotherapy with bevacizumab (15 mg/kg every 3 wk) was compared to the effects of pegylated IFN-α_{2b} (0.5 μg/kg per week) in patients with advanced carcinoid tumors. After 18 wk an almost 30% higher rate of progression free survival rate (PFS) was observed in the bevacizumab arm (98% PFS) as compared to the peg-IFN-α_{2b} arm (68% PSF) (NIH: NCT00055809). In bevacizumab-treated patients, CT scan, monitoring the antiangiogenic effects of bevacizumab at the individual patients´ level, showed a dramatic decrease in tumor perfusion. Based on these encouraging findings a phase Ⅲ trial is currently being proposed to evaluate the benefit of bevacizumab as compared to IFN-α_{2b} for the treatment of patients with advanced carcinoid tumors and a poor-prognosis who are under stable doses of depot octreotide (South West Oncology Group; unpublished study-protocol of study: S0518).

Several other studies using bevacizumab for combination therapy of GEP NET are currently ongoing.

Table 1 Current status of clinical trials with agents that target growth factor receptors and related signaling pathways for treatment of gastrointestinal neuroendocrine tumors

Name	Target	Mechanism	Tumor type	Cotreatment	Status	Reference
Bevacizumab	VEGF	VEGF-neutralizing antibody	Carcinoid	Peg IFN-α	Phase Ⅱ	[35]
			Carcinoid	Depot-octreotide	Phase Ⅲ	South West Oncology Group: S50518
			Carcinoid	Panzem	Phase Ⅱ	NCT00227617
			Advanced GEP NET	FOLFOX	Phase Ⅰ/Ⅱ	NCT00328497
			Advanced GEP NET	Oxaliplatin, capecitabine	Phase Ⅱ	NCT00398320
			Pancreatic and other unresectable carcinoid	Temzolomide	Phase Ⅱ	NCT00137774
Sunitinib	VEGFR, PDGFR, c-KIT, FLT3	Tyrosine kinase inhibitor	Carcinoid		Phase Ⅱ	[48]
			Carcinoid		Phase Ⅱ	NCT00428597
			Carcinoid[1]		Phase Ⅱ	NCT00434109
Pazopanib	Pan-VEGFR, PDGFR, c-KIT	Tyrosine kinase inhibitor	Low-, intermediate grade GEP NET		Phase Ⅱ	NCT00454363
AMG706	pan-VEGFR, PDGFR, c-KIT	Tyrosine kinase inhibitor	Low-grade GEP NET		Phase Ⅱ	NCT00427349
Vatalanib	VEGFR, PDGFR, c-KIT	Tyrosine kinase inhibitor	Progressive GEP NET[2]		Phase Ⅱ	[64]
			Progressive GEP NET		Phase Ⅱ[3]	NCT00227773
Gefitinib	EGFR	Tyrosine kinase inhibitor	Progressive GEP NET		Phase Ⅱ	[79]
			Advanced GEP NET	Cetuximab	Phase Ⅱ	NCT00397384
NVP-AEW541	IGF-1R	Tyrosine kinase inhibitor	NET cells		Pre-clinical	[14]
Everolimus	mTOR	Protein kinase inhibitor	Islet carcinoid		Phase Ⅱ	[136]
			Carcinoid	Octreotide	Phase Ⅱ	[127]
Temsirolimus	mTOR	Protein kinase inhibitor	Recurrent, metastatic GEP NET		Phase Ⅱ	[137]
Sorafenib	c-Raf, B-Raf, VEGFR, PDGFR	Tyrosine kinase inhibitor	Progressive, metastatic GEP NET		Phase Ⅱ	NCT00131911
Imatinib	PDGFR, c-KIT, ABL	Tyrosine kinase inhibitor	Carcinoid		Phase Ⅱ	[127]
			Advanced GEP NET		Phase Ⅱ	[59]
Bortezomib	Proteasome	Proteasome inhibitor	Metastatic GEP NET		Phase Ⅱ	[153]

[1]Liver predominant metastases after hepatic arterial embolization; [2]Progressive after somatostatin treatment; [3]Withdrawn.

A pending Phase Ⅰ/Ⅱ trial is recruiting patients with advanced neuroendocrine tumors to determine the safety and efficacy of bevacizumab in combination with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) (NIH: NCT00227617). Additionally, the efficacy of bevacizumab together with oxaliplatin and capecitabine is currently being investigated in metastatic and unresectable GEP NETs in a non-randomized, open label phase Ⅱ trial (NIH: NCT00398320). Bevacizumab is also being tested in combination with 2-methoxyestradiol (Panzem) in patients with locally advanced or metastatic carcinoid tumors (NIH: NCT00328497). Panzem is a metabolite of estradiol that has recently emerged as a promising anticancer agent because of its potent growth-inhibitory and proapoptotic effects on both endothelial and tumor cells[34,35]. Besides other antiangiogenic and cytotoxic properties panzem's mode of action involves the inhibition of the hypoxia-inducible factor (HIF)-1α, a transcription factor, which drives the expression of several pro-angiogenic genes[36]. *In vitro* and *in vivo* (animal) studies of several tumor types, including sarcoma, lung, and breast cancer, have documented potent inhibitory effects on tumor cells and angiogenesis without major clinical signs of toxicity[37]. Thus, a dual targeting of GEP NETs at the level of both the tumor cell and tumor microvessel formation by panzem and bevacizumab appears to be a promising combination.

Another interesting phase Ⅱ trial currently explores the combination of bevacizumab and the DNA-methylating drug temzolomide (NIH: NCT00137774). The rationale for this particular combination is based on findings of a former phase Ⅱ trial, in which an enhanced antitumoral efficacy of a combination treatment with temzolomide together with the mildly antiangiogenic VEGFR- and bFGFR- inhibitor, thalidomide, was demonstrated for advanced pancreatic GEP NETs and metastatic carcinoid tumors[38]. However, thalidomide is considered a risky drug that has been associated with neurological side effects and severe and frequent teratogenicity in the 1950s and 1960s[39]. Thus, in order to replace thalidomide by a safer antiangiogenic drug, bevacizumab is now being studied as a combination partner for temzolomide.

Anti-PlGF treatment

The use of a neutralizing anti-PlGF monoclonal antibody in VEGF-inhibitor resistant tumors is an attractive new antiangiogenic that has been tested in an animal study[40]. The antibody specifically inhibits the binding of PlGF to its receptor VEGFR-1, present on tumor associated endothelial cells and macrophages. The underlying idea of

using this approach derives from gene inactivation studies showing that endogenous PlGF is redundant for vascular development and physiological vessel maintenance, but an important contributor to the "angiogenic switch" in solid tumor growth. This lead to the hypothesis that unlike VEGF inhibitors, PlGF inhibition might reduce pathological angiogenesis, without affecting physiological blood vessel homeostasis and thus not causing unwanted side effects. Hence, anti-PlGF treatment could perhaps substitute for anti-VEGF therapy in the future. Moreover, as PlGF levels are known to increase in the circulation of cancer patients receiving anti-VEGF treatment[41-43], anti-PlGF could also counter this potential downside of anti-VEGF therapy. In this line, the data on inhibition of angiogenesis, lymphangiogenesis, tumor growth and motility in the anti-PlGF-treated anti-VEGF-resistant tumor bearing mice are impressive, especially with regard to blocking the so-called rescue-angiogenesis, a major problem in current antiangiogenic approaches, together with an excellent tolerability compatibility of the treatment. In addition, anti-PlGF treatment may permit long-term treatment of cancers in children, pregnant women, or patients at risk for thrombotic, cardiac or other complications for whom the adverse effects of other VEGF/VEGFR-inhibitors may be excessive and prohibitive.

Antiangiogenic therapy with small molecule inhibitors

In addition, several agents, which inhibit the tyrosine kinase activity of angiogenic growth factor receptors like the VEGFR or PDGFR, have been synthesized by combinatorial chemistry. These tyrosine kinase inhibitors are small molecules that occupy the ATP binding site of the tyrosine kinase domain of the intracellular portion of the receptor. Because of their effects on downstream signaling, these inhibitors interfere with a number of key biologic functions associated with VEGFR activation. Although drugs that are directed to the VEGFR proved their clinical efficacy, the redundancy in the angiogenesis pathways will likely necessitate multiple targeting agents appealing[44].

SUNITINIB

Recent clinical studies showed remarkable growth suppression of several non-GEP NET tumors by sunitinib, an orally available inhibitor of multiple receptor tyrosine kinases such as VEGFR-, PDGF-βR, c-KIT and FLT-3. Sunitinib has been approved for the treatment of renal cell carcinoma[45]. With restricted indication sunitinib is also approved for the therapy of gastrointestinal stromal tumors (GIST)[46] and is currently tested in phase I and II trials for hepatocellular carcinoma (NIH: NCT00361309; NCT00247676).

In GEP NETs, a phase II trial reported partial responses of 15% in pancreatic islet cell carcinoma and 2% in carcinoid tumors. In both groups, a high rate of disease stabilization, 75% for islet tumors and 93% for carcinoid tumors, was observed[47,48]. Based on these encouraging results an international randomized and double-blind phase III trial has been launched to study the effect of sunitinib given daily as a continuous dose versus placebo in patients with advanced carcinoids and islet cell tumors (NIH: NCT00428597). In a single-center, non-randomized, prospective phase II trial GEP NET patients with liver-predominant metastases are currently recruited to investigate sunitinibs efficacy to improve time to liver cancer progression following hepatic arterial embolization (NIH: NCT00434109).

PAZOPANIB AND AMG706

These two orally available drugs are pan-VEGFR inhibitors, which also block the activity of the PDGFR and c-kit. Antineoplastic activity of AMG706 has been shown in preclinical non-NET models[49]. Good tolerability and antitumor efficacy have been observed in first clinical trials with advanced refractory solid tumors[42]. Additional studies of AMG706 as monotherapy and in combination with various agents are ongoing[42,50]. At present, a clinical study assesses the efficacy of a monotherapy with AMG706 in patients with low-grade NET (NIH: NCT00427349). The primary goal of the trial is to evaluate the tolerability and 4-mo progression free survival under AMG706 treatment.

For pazopanib (GW786034) an excellent antiangiogenic effect on both tumor cells and tumor associated endothelial cells has been shown in pre- and early clinical studies, and good tolerability has been reported in patients with ovarian- and advanced renal cell carcinoma[51,52]. Currently a phase II trials is recruiting patients to evaluate the suitability of pazopanib for the treatment of advanced low-grade or intermediate-grade NET (NIH: NCT00454363).

IMATINIB

The phenylaminopyrimidine derivative Imatinib mesylate (Gleevec) is an orally available small molecule that selectively inhibits the tyrosine kinases ABL, c-Kit and PDGFR. Due to its ABL- and c-Kit-inhibiting potency, imatinib has significantly improved the treatment of cancers that crucially depend on the activation of these growth factor receptors, such as chronic myelogenous leukemia and gastrointestinal stromal tumors[53,54]. Moreover, imatinib demonstrated clinical efficacy by inhibition of PDGFR-signaling in dermatofibrosarcoma protuberans, a neoplasm that depends on an abnormal activation of PDGFRβ through an autocrine loop[55].

Although there have been no reported mutations in ABL, c-Kit, and PDGFR in NET, they are characterized by a simultaneous upregulation of PDGF ligands and their receptors (PDGFR-α and PDGFR-β)[6,56,57]. Thus, imatinib may also be interesting for GEP NET treatment. Yao and coworkers evaluated this hypothesis in a phase II trial of patients with advanced carcinoids who were treated with 400mg imatinib twice daily. However, only one of the 27 treated patients achieved an objective response, while 17 patients had stable disease, and 9 patients showed disease progression when evaluated with RECIST criteria (Response Evaluation Criteria in Solid Tumors)[58]. Another

study that included 15 patients with advanced GEP NET, imatinib (400 mg or 800 mg imatinib/day for up to 12 mo) was not effective, but was associated with remarkable toxicity and increased bleeding tendency[59].

The low response rate to imatinib, as compared to other antiangiogenic agents, may be related to its sole activity towards the PDGFR, while it completely lacks VEGFR-inhibitory activity. Moreover, PDFGR-inhibition by imatinib is relatively low, as compared to other PDGFR-targeting agents. For instance, the small molecule inhibitor sunitinib has a tenfold higher potency to inhibit PDGFR-signaling, and moreover also inhibits VEGFR-signaling.

From the data obtained so far, monotherapy with imatinib does not seem to be beneficial for patients with advanced GEP NET. Future trials will have to focus on imatinibs suitability as an additive agent for combination therapy, e.g. in conjunction with VEGFR-inhibitors[60].

VATALANIB

Vatalanib (PTK787/ZK222584) inhibits the activities of VEGFR-1 and -2 tyrosine kinases and shows antineoplastic effects in several solid tumors[61-63]. This oral agent achieved a 25% biochemical partial response rate (defined as > 50% decrease in 5-HIAA) in NET patients with progressive disease following unsuccessful somatostatin-analog therapy[64]. Although partial radiographic responses have not been observed, further recruitment for this phase Ⅱ trial is currently ongoing. By contrast, another phase Ⅱ trial investigating vatalanib alone and in combination with somatostatin analogs for the treatment of progressive NET has only recently been withdrawn (NIH: NCT00227773). At present, it is unclear if this was due to insufficient antitumoral activity, toxicity or other reasons.

EGFR-BASED STRATEGIES

The crucial role of epidermal growth factor receptor (EGFR) in tumor proliferation and its overexpression in several solid tumors have provided the rationale for targeting and interrupting this key signaling network. EGFR blockade with monoclonal antibodies and tyrosine kinase inhibitors has translated into clinical benefit in gastrointestinal tumors, particularly colorectal cancer[65].

Over the past few years, three EGFR-specific agents have received regulatory approval: (1) The monoclonal anti-EGFR antibody cetuximab for metastatic colorectal cancer, and squamous cell carcinoma of the head and neck; (2) The tyrosine kinase inhibitor erlotinib for advanced or metastatic pancreatic cancer and NSCLC; and (3) The EGFR tyrosine kinase inhibitor gefitinib for advanced or metastatic NSCLC. However, the general FDA approval for NSCLC treatment with gefitinib was recently withdrawn after it failed to demonstrate a survival benefit either alone or with chemotherapy in three phase Ⅲ trials[66,67].

Several reports indicate that EGFRs are frequently expressed and upregulated in NET in general[68,69], as well as in gastrointestinal NET[70-75]. In addition, EGFR contributes to the growth characteristics of GEP NETs[76-78]. Hence, the EGFR is an attractive target for GEP NET disease, and EGFR-inhibitors have already been shown to inhibit GEP NET cell growth *in vitro*[13].

Despite the encouraging preliminary findings on the general suitability of anti-EGFR-based-approaches for the treatment of GEP NET[13,78], no clinical trials have been conducted so far, while their efficacy has been demonstrated in other tumor entities, especially colorectal cancer, renal cell carcinoma and NSCLC.

Hobday and coworkers now conducted a phase Ⅱ trial of gefitinib monotherapy in patients with progressive GEP NET. The study showed that gefitinib is well tolerated and prolongs disease stabilization in patients with prior documented objective progression of islet cell carcinoma and carcinoid tumors. The 6-mo progression free survival of gefitinib-treated patients was 30% for carcinoid tumors and 10% for islet cell carcinoma. However, no objective responses have been observed[79].

In another ongoing trial the efficacy of a combination treatment with the EGFR-TK inhibitor, erlotinib[80], together with the EGFR-antibody, cetuximab[81], is currently evaluated in patients with advanced gastrointestinal cancers, including carcinoid tumors (NIH: NCT00397384). The rationale for the combination of two EGFR-targeted agents is that erlotinib may stop the growth of GEP NET cells by blocking essential growth-related signaling pathways, while cetuximab may additionally mark GEP NET cells with IgG for attack by immune effector cells[82]. Moreover, erlotinib and cetuximab are thought to stop the growth of GEP NET cells also by antiangiogenic effects on the tumor endothelium.

Anti-EGFR-based therapies have their greatest potential in combination either with conventional cytostatics or with other targeted-agents[81,83-85]. Again, the rationale for using combination therapies is the existence of multilevel receptor cross-stimulation or of redundant signaling pathways that lead to neoplasia. Blocking only one of these pathways allows others to act as salvage or escape mechanisms for cancer cells. Preclinical evidence of synergistic antitumor activity achievable by combining targeted agents that block multiple signaling pathways has recently emerged[17,86]. The multi-target approach can be accomplished by using either combinations of selective agents or single agents, which interfere with various targets[18].

IGF/IGFR-BASED STRATEGIES

Both insulin-like growth factors, IGF-Ⅰ and -Ⅱ, and their receptor tyrosine kinase, IGF-1R, are involved in the development and progression of cancer[87-90]. Activation of the IGF-1R by IGF-Ⅰ and -Ⅱ plays a pivotal role in tumor cell proliferation and spread, by promoting cell cycle progression, preventing apoptosis, and by regulating and maintaining the metastatic tumor phenotype. A wide variety of tumors including GEP NET show abnormal or enhanced expression of IGFs and IGF-1R, which leads to auto- and paracrine growth stimulation, and which has been correlated with enhanced proliferation, tumor de-differentiation, disease stage, development of metastases and reduced patient survival. In GEP NET, the dysregulation of the IGF/IGFR system also contributes

to the excessive secretion of biogenic amines[8,91-95]. In gastrinoma patients, the increased expression of the IGF/IFGR-system is associated with low curability and the development of metastases[96,97]. Thus, the inhibition of the functionally upregulated IGF/IGFR-signaling system is a promising novel approach to treat GEP NET.

Several groups have demonstrated the therapeutic potential of interfering with IGF-1R mediated signaling *in vitro* and *in vivo*, including the use of IGF-1R blocking antibodies, IGF-1R antisense oligonucleotides, or IGF-1R siRNA[98-101]. Recently, we and others validated the potent and selective IGF-1R tyrosine kinase inhibitor NVP-AEW541 as a promising novel agent for the therapy of several cancers[102-104], including GEP NET[14]. The antineoplastic properties of NVP-AEW541 and related compounds such as NVP-ADW742 have been demonstrated in preclinical studies on Ewing's sarcoma-bearing mice, fibrosarcoma, breast cancer, and musculoskeletal carcinoma[105-109]. Specific IGFR-antibodies potently suppressed prostate and breast cancer cell growth *in vitro*[110]. The clinically most advanced anti-IGFR antibody is CP-751 871, which is currently being tested in three phase Ⅱ trials for advanced breast cancer, NSCLC and prostate cancer (www.clinical-trials.gov). Importantly, the preliminary clinical studies indicate that IGFR-inhibition is well tolerated[106,111,112]. Safety is important, since IGFR-based inhibition has long been regarded as a high-risk intervention, because of the high homology of the IGF-1R receptor with the related insulin-receptor, and the fear that IGF-1R tyrosine kinase inhibitors may lead to insulin resistance and overt diabetes[113]. However, the current *in vivo* data do not support this assumption, resulting in a growing interest in anti-IGFR-based therapies[114].

Due to crosstalk between the signaling of the IGF/IGFR system and other growth factor receptors that can attenuate the antineoplastic effect of monotherapeutic approaches, IGF/IGFR-targeting therapies will likely have to be combined with other therapies to enhance efficacy[115,116]. This can be achieved by dual-targeting the EGFR- and the IGF-1R, since the EGFR is activated by the IGF/IGFR-system leading to mito-oncogenic EGFR-tyrosine kinase activity without ligand stimulation of the EGFR[20]. In this line IGFR- combined with EGFR-inhibition can over-additively enhance the antineoplastic effect of the respective monotherapies in gastrointestinal cancers[81,83,104].

DUAL-TARGETING SMALL MOLECULE INHIBITORS

The use of dual-targeting small molecule inhibitors, simultaneously blocking less related kinases such as VEGFR and EGFR tyrosine kinases, may also become promising for future treatment of GEP NET. These agents inhibit both tumor cell proliferation/survival by blocking mito-oncogenic EGFR signaling of the tumor cells and angiogenesis by inhibiting endothelial VEGFRs. In recent *in vivo* studies of non-GEP NET tumor models (colon, cholangiocarcinoma, prostate, NSCLC) the dual-targeting tyrosine kinase inhibitor NVP-AEE788 displayed significant antineoplastic efficacy[117-120]. Also for ZD6474 (zactima), another EGFR/VEGFR tyrosine kinase inhibitor, promising phase Ⅱ/Ⅲ results were reported for NSCLC and thyroid cancer showing response rates of 30% in patients with locally advanced medullary thyroid cancer[121] as well as significant prolongation in the progressive free survival of NSCLC patients[122,123]. Furthermore, dual targeting of the EGFR and the insulin like growth factor receptor are promising new approaches for the treatment of solid tumors, including the GEP NETs[116].

OTHER STRATEGIES

Targeting the 'mammalian target of rapamycin' (mTOR) pathway

The activated PI3K/AKT/mTOR pathway has emerged as a novel contributor to (GEP NET-) tumor development. PI3K associates with the intracellular domain of several growth factor receptors. Upon receptor activation, PI3K triggers the generation of phosphatidylinositol 3,4,5-trisphosphate (PIP3), which provokes the subsequent activation of AKT, a serine/threonine kinase that activates multiple cellular target proteins, such as the mammalian target of rapamycin (mTOR) subfamily. mTOR is a serine-threonine kinase that regulates apoptosis, proliferation and cell growth by modulating cell cycle progression. Specifically, mTOR is involved in the modulation of mRNA-translation of proteins, which are necessary for cell cycle progression from G1 to S-phase, including the E4-binding protein (E4-BP1), and $p70^{S6}$ kinase[124].

In nontransformed cells the PI3K/AKT/mTOR pathway is controlled by the phosphatase and tensin homolog deleted on chromosome ten (PTEN), a tumor suppressor which inhibits this pathway by reversing PI3K and subsequent AKT activation. Mutation or silencing of the PTEN gene leads to activation of the mTOR pathway and promotes carcinogenesis. Loss of PTEN expression has been shown in GEP NET[125]. Accordingly, in sporadic islet cell carcinoma a frequent loss of 10q, the site of the PTEN gene, as well as an altered subcellular localization of PTEN have been reported[126,127]. Thus, constitutive activation of the PI3K/AKT/mTOR pathway can be due to enhanced stimulation of growth factor receptors, like EGFR and IGFR, but also to decreased PTEN expression or to its altered cellular compartmentalization[128]. Importantly, 76% of all GEP NETs display constitutive AKT phosphorylation[78,125]. It is therefore likely that a majority of GEP NET is sensitive to mTOR inhibitors. Indeed, antiproliferative effects of mTOR inhibition in GEP NET cells were recently demonstrated *in vitro*[129].

mTOR-inhibitors

The natural antibiotic rapamycin (sirolimus) is a potent inhibitor of mTOR[130]. Recently, three analogues of rapamycin with superior pharmacokinetic and biological properties have emerged. The cell cycle inhibitor-779 (CCI-779, temsirolimus) is a soluble ester analogue. RAD001 [40-O-(2-hydroxyethyl)-rapamycin, everolimus] is

a derivative of rapamycin with high oral bioavailability, and AP23573 is a non-pro-drug analogue of rapamycin. These agents have been tested successfully for their antineoplastic potency and/or tolerability in various malignancies in early clinical trials (e.g. CCI-779 in renal, breast and lung cancers), or are currently being studied in open clinical trials for the treatment of colorectal, endometrial, and brain tumors (RAD001, everolimus)[131-133]. AP23573 has been successfully tested in a phase Ⅱ trial in sarcomas[134] and two phase I studies in patients with refractory or advanced solid tumors showed partial responses and disease stabilization in individual patients[135].

So far, two-phase Ⅱ trials exploring mTOR-inhibitors for NET treatment have been reported. Studies with everolimus (RAD001)[136] and temsirolimus (CCI-779)[137] have recently completed the recruitment of low-grade NET patients.

The study by Yao *et al*, reported on 32 patients (18 carcinoids, 13 islet cell carcinomas) who had received 5 mg everolimus orally per day and depot octreotide 30 mg intramuscularly every 28 d. After 12 wk of treatment, the evaluation by RECIST criteria (response evaluation criteria in solid tumors) showed a 15% response. There were four patients with partial response, 22 with stable disease and 4 patients with progressive disease. Progression occurred in two carcinoids and two islet-cell carcinomas. The rate of progression free survival (PFS) at wk 24 was 64% and the treatment was generally well-tolerated[136]. The promising results of this study led to the development of a multicenter phase Ⅱ study, RADIANT (RAD001 in advanced NET), in which everolimus (RAD001) is investigated as second-line treatment in patients with advanced pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy. A similar phase Ⅱ trial has been activated to evaluate RAD001 in patients with carcinoid tumors[127]. In both cases, RAD001 will be used as a monotherapy and in combination with octreotide, which inhibits the activated IGF/IGFR pathway of GEP NET. The underlying rationale is that the dual inhibition of mTOR activation by directly targeting mTOR with everolimus, and also its upstream activation *via* IGF/IGFR-signaling with octreotide will completely abrogate this important pathway in NET. This assumption is supported by *in vitro* data that demonstrated the antiproliferative potency of the dual inhibition of endogenous and IGF-stimulated mTOR activity of GEP NET cells by rapamycin[8].

In the other phase Ⅱ trial[137], the clinical and pharmacodynamic effects of the temsirolimus, were investigated in 37 patients with recurrent or metastatic GEP NET. However, temsirolimus showed only modest activity accompanied by distinct but manageable drug-related adverse effects (mainly fatigue, hyperglycemia, rash). The authors concluded that based on the sobering results of this study no further investigation of temsirolimus as a single agent in patients with advanced GEP NET was justifiable. However, evaluation of temsirolimus in combination with other targeted agents, such as multi-kinase inhibitors or antiangiogenic compounds, was suggested[124].

Targeting the Ras/Raf/MAPK pathway

The proliferative Ras/Raf/MEK/ERK pathway is one the key signaling cascades that underlie the development and maintenance of cancers. This pathway transduces extracellular signals from the various growth factor receptor tyrosine kinases (e.g. EGFR, IGFR, VEGFR, PDGFR) to the nucleus with a series of specific phosphorylation events, resulting in the expression of proteins for cell cycle progression, apoptosis resistance, extracellular matrix remodeling, cellular motility, angiogenesis or drug resistance[138]. Dysregulation of this crucial pathway occurs due to oncogenic transformation of Ras and Raf isoforms, or to overexpression and/or overactivation (*via* phosphorylation) of the Ras and Raf genes[139,140]. Although activating mutations of (B)-Raf are rare in GEP NET[141], wildtype B-RAF and its activating small G-protein Rap-1 are highly prevalent in the majority of GEP NET. Overexpression of Rap-1 was shown to activate MAPK-signaling and the expression of mitogenic transcription factors of GEP NET cells, thus providing an interesting molecular target for GEP NET treatment[142].

SORAFENIB

The bi-aryl urea derivative sorafenib (nexavar™) is an oral multi-kinase inhibitor, which targets kinases of wild-type B-Raf, mutantV559EB-Raf and C-Raf, and importantly receptor tyrosine kinases involved in angiogenesis, including VEGFR-2, and -3, and PDGFR[143]. Sorafenib has been approved by the FDA for the treatment of advanced renal cell carcinoma, and only recently it gained accelerated approval for the treatment of inoperable hepatocellular cancer.

Sorafenib's effect on several molecular targets in addition to the Raf isoforms makes it difficult to determine which of its targets contributes most to the anti-tumor activity of sorafenib in the particular tumor types. For instance, a recent HCC trial suggested that inhibition of the Raf/MEK/ERK pathway was central to sorafenib's mode of anti-tumor action[144], whereas in other cancers, such as renal cell carcinoma or NSCLC the antineoplastic activity was attributed mainly to its antiangiogenic activity[16,145]. In 2005, an international multicenter phase Ⅱ trial has started to evaluate the efficacy of sorafenib in patients with progressive metastatic NET (NIH: NCT00131911). Results from this study, which enrolled 90 patients, are pending.

Targeting the proteasome

Effective cancer treatment may also be achieved by inhibition of the 26S proteasome, a large protease complex that is present in both the nucleus and the cytoplasm of eukaryotic cells. The proteasome functions as a proof-reader and terminator of proteins branded for destruction by the attachment of ubiquitin. The so-called ubiquitin-proteasome pathway (UPP) is the major non-lysosomal proteolytic system in eukaryotic cells and triggers degradation of a multitude of proteins, including those involved in cell cycle progression, apoptosis, nuclear factor kappaB (NF-κB) activation, and angiogenesis, as well as

mutant, damaged, and misfolded proteins[146]. Inhibition of the proteasome has emerged as an attractive target for cancer therapy, since a functional UPP is critical for cell survival and proliferation, especially of cancer cells.

BORTEZOMIB

Bortezomib (Velcade™) blocks multi-ubiquitinated protein degradation by inhibiting the active site threonine residue of the 26S proteasome in a competitive and reversible manner[147]. Antineoplastic activity of bortezomib has been documented in several *in vitro* and *in vivo* studies[148-150], including NET cells[151]. Bortezomib is the first proteasome inhibitor that has been approved for treatment of advanced multiple myeloma and mantle cell lymphoma[146,152].

So far, only one clinical study on bortezomib in advanced metastatic GEP NET has been reported. However, in contrast to the encouraging findings in other cancers, no or only marginal responses to bortezomib monotherapy was observed in the investigated 12 carcinoid and 4 islet carcinoma patients. Given the slow growing nature of these tumors, the observed disease stabilization of 69% (11 of 16 patients) could not be attributed unequivocally to an antitumor effect of bortezomib. Although bortezomib was generally well-tolerated, peripheral sensory neuropathy developed in 37% of the patients[153]. Specific attention has to be paid to such side effects, when bortezomib (or other targeted agents) are to be combined with other antitumoral drugs, especially conventional chemotherapy, which likely increases gastrointestinal or neurologic toxicity.

Moreover, bortezomib has been combined with multi-kinase inhibitors or histone deacetylase inhibitors (HDAC). Especially, the combination of bortezomib with HDAC inhibitors appears to be a promising approach in GEP NET disease. Baradari and coworkers showed that HDAC inhibition had strong antiproliferative and proapoptotic effects in GEP NET cells[154]. Recently, the potency of bortezomib combined with HDAC inhibitors has been demonstrated for other gastrointestinal tumors, too. Thus, HDAC inhibition by the benzamide derivative, MS-275 combined with bortezomib led to an overadditive growth inhibition of cholangiocarcinoma cells[148]. Hence, targeting two or more molecular pathways at the same time appears promising for innovative treatment strategies of GEP NET disease.

CONCLUSION

Targeted-therapies, which specifically inhibit growth factor receptors and their related signaling pathways are promising approaches for the innovative medical treatment of GEP NET disease. Especially antiangiogenic strategies, multi-kinase or mTOR inhibition as well as combination treatments with biotherapeutics or cytostatics emerge to prove particularly efficient, as they leave fewer mechanisms of escape for the tumor cells. Combinations of these targeted drugs are particularly intriguing, and in the future agents like the multi-kinase inhibitors sunitinib or sorafenib as well as mTOR inhibitors will be combined with other growth factor receptor inhibitors, histone deacetylase inhibitors, proteasome inhibitors, biotherapeutics or cytostatics to effectively control advanced GEP NET. The advantage of such novel combination therapies is their higher tumor cell specificity and higher efficacy, combined with acceptable toxicity and side effects. The novel combination treatments will widen the therapeutic spectrum for GEP NET; the results of (ongoing) clinical studies are eagerly awaited.

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