Virchows Arch (2007) 451 (Suppl 1):S71–S80
DOI 10.1007/s00428-007-0446-z

REVIEW AND PERSPECTIVE

Treatment of gastroenteropancreatic neuroendocrine tumors

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Received: 16 May 2007 / Accepted: 6 June 2007 / Published online: 8 August 2007

Abstract Neuroendocrine tumors are rare; thus, individual experience with the diagnosis and treatment of these tumors is mostly low, except in specialized centers. For histological diagnosis, standards have been described recently. Pathological classification and clinical staging influence diagnostic and therapeutic decisions. This chapter aims at demonstrating the importance of pathological and clinical classification of neuroendocrine tumors on therapeutic decisions, indicating the appropriate therapy for different stages of the disease. Surgical therapy will be discussed shortly, including palliative surgical strategies. However, the focus of the manuscript is medical therapy. Biotherapy, its effects, and remaining uncertainties are presented as well as different chemotherapeutic schemes. Finally, new options of palliative medical therapies like kinase inhibitors and anti-angiogenetic drugs will be discussed.

Keywords Gastroenteropancreatic neuroendocrine tumors · Biotherapy · Somatostatin analogue · Interferon · Chemotherapy · Streptozotocin · Tyrosine kinase inhibitor · Anti-angiogenic therapy

Introduction

Neuroendocrine tumors are classified according to their differentiation, localization, and functionality. The pathological classification and the stage of the tumor disease have important prognostic implications and, thus, influence therapeutic decisions. This chapter starts with a brief discussion of surgical options, then focuses on the established indications of bio- and chemotherapy in gastroenteropancreatic neuroendocrine tumors of the foregut and midgut. Finally, the evolving new therapeutic options are discussed.

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Surgery

Surgery is the only curative therapy available in gastroenteropancreatic neuroendocrine tumors. Unfortunately at diagnosis, most tumors have already metastasized, and thus, surgery is rarely curative. Surgery is rarely indicated in patients with small (<1 cm) gastric neuroendocrine tumors type 1 or type 2, due to the mostly benign course of the disease. In contrast, oncological resection of the tumor is imperative in malignant type 3 gastric neuroendocrine tumors [53, 54, 58]. Duodenal and pancreatic primaries are both indications for surgical therapy. However, palliative surgery of the primary, in patients with inoperable hepatic metastasis, has no positive effect on survival. It has been suggested, that palliative surgery of hepatic metastases, either in combination with surgical therapy for the primary or following R0-resection of the primary tumor, does prolong survival in patients with pancreatic or midgut neuroendocrine tumors. All series so far are, however, retrospective analysis of monocentric experiences, and selection bias has to be taken into account. Surgical intervention for hepatic metastasis, without removal of the primary, is not recommended. In general, surgical therapy adheres to oncological principles [12, 22, 30, 31, 49, 53]. However, for appendiceal neuroendocrine tumors due to the excellent prognosis of small (<2 cm) tumors, appendectomy is now considered curative, and right hemicolectomy is indicated only in tumors larger than 2 cm with deep mesoappendiceal invasion [53].

Further, more palliative treatment options such as radiofrequency ablation, chemo-embolization of liver metastases, and peptide radio-receptor therapy have been reviewed recently and will not be discussed here [53].

Medical therapy

Biotherapy can be used as a symptomatic treatment in patients with functioning neuroendocrine tumors, i.e., in patients with the carcinoid syndrome, watery diarrhea-, or glucagonoma syndrome. Symptomatic therapy for insulinomas is rarely necessary, as most of these tumors are benign, and thus, surgery is curative. The objective of symptomatic biotherapy is to reduce signs, symptoms, and complications of hormone hypersecretion syndromes and, thus, to increase the quality of life and overall survival. In addition, biotherapy has been used as an antiproliferative treatment in slow-growing malignant, well-differentiated (World Health Organization classification), metastasized neuroendocrine carcinomas. While tumor regression is rare, stabilization of tumor growth has been demonstrated.

Most gastroenteropancreatic neuroendocrine tumors present with malignant, metastatic disease. Chemotherapy is a palliative option in both slow-growing, well-differentiated, or rapidly proliferating, poorly differentiated, neuroendocrine tumors. In slow-growing, well-differentiated tumors, tumor growth is unpredictable, and slow tumor progression may alternate with long intervals of stable disease. As the quality of life is good in most patients with metastasized well-differentiated neuroendocrine tumors, antiproliferative therapy should only be initiated whenever progressive disease has been demonstrated according to standard criteria. While different treatment regimens have been shown to be effective in well-differentiated pancreatic neuroendocrine carcinomas, chemotherapeutic options for tumors of the small bowel are poor. Localization of the primary is not as important for poorly differentiated carcinomas, as these rapidly growing tumors respond to different chemotherapeutic agents, irrespective of the localization of the primary. These tumors may grow rapidly, and medical treatment should not be withheld to demonstrate progressive disease.

Biotherapy

Biotherapy is defined as the therapy for hormonal hypersecretion syndromes and/or tumor growth with substances or pharmacological derivatives thereof occurring naturally in the body. Despite the widespread therapeutic use of biotherapy in neuroendocrine tumors, data fulfilling the criteria of evidence-based medicine are rare. The interpretation of study results has to be done with some caveats. Data referring to the therapeutic efficacy of biotherapy only rarely give primary endpoints like mortality or the time to progression. Most studies include a variety of neuroendocrine tumors, the number of patients is low, and most studies represent single center experience. The results of different studies are difficult to compare, as dosage, treatment duration, and a variety of different pretreatments were employed. There are only few prospective, randomized multicenter studies in therapy-naïve patients with documented progress before initiation of biotherapy. No placebo group was ever included in these studies. However, despite these drawbacks, there are indications of the benefit of biotherapy on symptoms of hormone hypersecretion, while on the other hand, definite data on the antiproliferative effectiveness and its positive effect on survival are still lacking.

Somatostatin analogues (SSA)

Endogenous somatostatin (SS) circulates in two biological active forms, i.e., SS-14 and SS-28. SS binds with high affinity to five G protein-coupled membrane receptors (sst1-5). Ligand binding inhibits adenylate cyclase activity, reduces calcium influx, and negatively influences hormone synthesis and secretion. An inhibitory influence on proliferation may be due to the activation of phosphotyrosine phosphatases, the mitogen-activated protein kinase activity [38], and to the inhibition of the transcription factor complex activator protein 1. In vitro, high doses of SSA induce apoptosis in tumor cells, and this could translate into inhibition of tumor growth. Additional antiproliferative effects may be related to the anti-angiogenic activity of SS either directly or via inhibition of growth factors [11]. Most neuroendocrine tumors express a higher density of sst in tumor tissue compared to the normal tissue. This allows for specific, tumor tissue-targeted, therapeutic effects and should reduce the number of side effects, i.e., suppression of physiologically secreted hormones. However, sst-subtype expression varies considerably between different tumor types and among tumors of the same type. Even within a given tumor, sst expression is not homogenously distributed [27].

The clinically used SSA, octreotide and lanreotide, preferentially bind to sst2 and sst5 (Table 1). For these analogues, serum half-life is increased considerably compared to native somatostatin. The subcutaneous injectable octreotide has to be given three times daily, while long-acting preparations, (lanreotide long-lasting and octreotide long-acting repeatable [LAR]), allow for one intramuscular injection every two (lanreotide) to four (octreotide LAR) weeks. In the case of lanreotide autogel, an interval up to 6 weeks between injections and the possibility to be injected by the patients themselves, may increase patients' comfort and compliance. Recently, pasireotide has been introduced, a

Table 1 Binding affinities of somatostatin analogues to somatostatin receptor (sst) subtypes

sst	SS-14	Octreotide	Lanreotide	Pasireotide
sst1	0.93±0.12	280±80	180±20	9.3±0.1
sst2	0.15±0.02	0.38±0.08	0.54±0.08	1.0±0.1
sst3	0.56±0.17	7.10±1.40	14±9	1.5±0.3
sst4	1.40±0.40	>1,000	230±40	>100
sst5	0.29±0.04	6.3±1.0	17±5	0.16±0.1

Binding affinities are given as mean±SEM IC-50 (nmol/l)

SSA with high affinity for sst1-3 and sst5. It has been shown to be effective in patients who do not respond to the currently available SSA octreotide and lanreotide. However, its use is still restricted to clinical studies.

Octreotide and lanreotide both effectively inhibit autonomous hormone or neurotransmitter secretion by neuroendocrine gastrointestinal tumors. Unfortunately, tachyphylaxis develops after months or even years of treatment in virtually all patients. Tachyphylaxis may be due to desensitization, homologous agonist-induced down-regulation in sst numbers on the cell surface, heterologous regulation of SS receptor expression, or even SS receptor gene mutations [27].

Indications for SSA therapy

SSA are indicated in patients with symptoms due to excessive, autonomous hormone release by a neuroendocrine tumor or its metastases. In patients with the carcinoid syndrome, octreotide LAR is equally potent in the control of flushing and diarrhea. SSA are indicated in the therapy of the watery diarrhea syndrome, reducing the secretion of vasoactive intestinal peptide, and thus, diarrhea, dehydration, and electrolyte imbalance. In patients with insulin hypersecretion, SSA may reduce the insulin concentration in tumors expressing sufficient sst2 or sst5, i.e., mostly malignant insulinomas. However, as SSA inhibit glucagon secretion as well, patients have to be observed closely at the beginning of therapy to prevent severe hypoglycemia due to the reduced glucagon-dependent counter-regulation. SSA effectively inhibit glucagon secretion in patients with a glucagonoma syndrome; skin lesions improve, and catabolism is reduced (Table 2).

SSA induce remission and/or stabilization of tumor markers in approximately 70% of the patients [46] (Table 3). The decline of tumor markers, like chromogranin A, is due to the anti-secretory effect of SSA and should not be interpreted as evidence for tumor volume reduction. Tumor shrinkage is demonstrated in less than 10% of the patients. However, stabilization of tumor growth, after computer tomographic-documented progression before treatment, occurs in up to 50% of the patients with neuroendocrine tumors of various locations. (Table 4). The median duration of stabilization was 18–26.5 months [3]. In a highly selected group of patients with progressive disease, forty-seven percent of the patients demonstrated at least stable disease when treated with a high dose of lanreotide (3×5 g/day). This was confirmed recently in 75% of the patients with advanced midgut carcinoids, with stabilization for 6 to 24 months. There are no good predictors of the clinical outcome of SSA therapy. Patients achieving a positive response (stabilization) after 6 months of treatment maintain it throughout long-term follow-up and live longer than patients unresponsive to therapy [50]. Frequently occurring side effects like abdominal discomfort, bloating, and steatorrhea due to the inhibition of pancreatic enzymes are mostly mild and subside spontaneously within the first weeks of therapy. Persistent steatorrhea can be treated with supplementation of pancreatic enzymes. Cholestasis with subsequent cholecystolithiasis does occur in up to 60% of the patients due to inhibition of cholecystokinin and production of lithogenic bile. Prophylactic therapy with chenodeoxy–cholic acid and ursodeoxy–cholic acid may be able to prevent the occurrence of gallstone disease in patients on long-term SSA therapy. Serum vitamin B12 concentration may decline, possibly due to a direct inhibition of the intrinsic factor secretion at the parietal cell [52].

In summary, SSA effectively control symptoms of hypersecretion in patients with neuroendocrine tumors of the gastrointestinal tract. Despite the minor effects on tumor volume reduction observed so far, an antiproliferative effect does occur, with stabilization of the disease for up to

Table 2 Effects of somatostatin analogues on hypersecretion syndromes

Syndrome	Symptom	Hormone/ neurotransmitter	Tumor marker
Carcinoid syndrome	Flush≥diarrhea	Serotonin	5-HIAA, CgA
Watery diarrhea syndrome	Diarrhea, dehydration, acidosis	VIP	VIP
Glucagonoma syndrome	Migratory necrolytic erythema	Glucagon	Glucagon
Insulin hypersecretion[a]	Fasting hypoglycemia	Insulin	Insulin
Zollinger–Ellison syndrome	Peptic ulceration, GERD	Gastrin	Gastrin

5-HIAA 5-Hydroxyindol-acetic acid; *GERD* gastro-esophageal reflux disease

[a] Benign insulinomas rarely express sufficient sst2 and 5 for SSA to be effective. Thus, SSA are only indicated as second-line therapy in malignant insulinomas (see text)

Table 3 Biochemical effect of somatostatin analogues

N	CR	PR	SD	PD	Author
23	0	9	5	9	[2]
39	2	11	15	11	[3]
13	4	6	3	9	[15]
14	0	9			[4]
89	6/89 (7%)	35/89 (39%)	23/75 (31%)	29/75 (39%)	

CR Complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease

25 months. Survival may be prolonged in those patients responding positively to SSA therapy. In addition, SSA significantly increase the quality of life in patients with symptoms related to hormone secretion, while side effects of SSA therapy are limited.

Interferon

Interferon-α 2a, or 2b (IFN) production is a physiological response to substances as microbes, tumor cells, and antigens. IFN react with specific cell surface receptors to activate a cytoplasmatic signal transduction cascade, inducing the transcription of multiple IFN inducible genes, which act as tumor suppressor genes. IFN-α acts on 2′ 5′-A-synthetase and p-68 kinase. Both enzymes induce the degradation of peptide hormone and growth factor messenger RNA, inhibiting protein synthesis. The induction of 2′ 5′-A-synthetase correlates with clinical efficacy. The antiproliferative effect of IFN is probably due to a blockade of the cell cycle in the transition of $G_0 \rightarrow G_1$ [45]. This is due to the inhibition of cyclin B expression, resulting in reduced CDC 2 kinase activity and, thus, inhibition of the cell cycle [13]. Furthermore, induction of apoptosis, as well as increased expression of class I antigens on the tumor cell surface (which marks the cell as a target for cytotoxic T lymphocytes) may add to the antiproliferative effects. In addition, an anti-angiogenic effect has been suggested.

IFN-α has been widely used for the treatment of solid tumors. In neuroendocrine tumors, the indications for IFN are comparable to those of SSA, with carcinoid crisis being the exception. However, there are only few data on the effect of IFN therapy in patients with pancreatic neuroendocrine tumors. Most investigations used recombinant IFN-α 2a or 2b.

Indications for IFN-α therapy

Symptomatic remission is seen in 30–70% of the patients with carcinoid syndrome, with a better effect of IFN therapy on flushing compared to diarrhea. While the control of symptoms of hypersecretion by IFN is comparable to SSA, its onset of response is delayed. A biochemical response is observed in 50% of the patients. Tumor marker remission or stable 5-HIAA concentration occurred in 36 and 35% of the patients, respectively. Analyzing results of ten clinical studies with mixed tumor populations (N=255), a partial remission or stabilization of tumor markers occurs in 44 and 30% of the patients, respectively. These data are comparable to a recent meta-analysis, with median response rates of biochemical markers in up to 44% of the patients

Table 4 Antiproliferative effect of somatostatin analogues in patients with progressive disease and in patients without documented progression

SSA	*N*	CR	PR	SD	PD	Author
In patients with progressive disease						
Lanreotide	22	0	1	7	14	[23]
Lanreotide	35	0	1	20	14	[2]
Octreotide	52	0	0	19	33	[5]
Octreotide	58	0	2	27	29	[15]
Octreotide	10	0	0	5	5	[3]
Lanreotide	24	1	1	11	11	[23]
	201	1 (0.5%)	5 (3%)	89 (44%)	106 (53%)	
In patients without documented progression						
Lanreotide	31	–	2 (7%)	25 (81%)	4 (13%)	[68]
Lanreotide	39	–	4 (10%)	19 (49%)	16 (41%)	[18]
Lanreotide	19	–	1 (5%)	12 (63%)	6 (32%)	[20]
Lanreotide	18	–	–	14 (78%)	4 (22%)	[66]
Octreotide	16	–	–	14 (88%)	2 (12%)	[65]
Octreotide	15	–	1 (7%)	6 (40%)	8 (53%)	[56]
Octreotide/lanreotide	13	–	4 (31%)	1 (8%)	8 (61%)	[1]
	183	0 (0%)	12 (8%)	91 (60%)	48 (32%)	

[60]. Tumor shrinkage occurs in 10% of the patients, whereas stable disease is observed in up to 70%. Progressive disease was seen in 23% of the patients. Table 5 gives data on a large cohort of patients with evaluable results on tumor mass (N=274) treated with IFN in ten studies. The median survival was >80 months. Again, the data should be interpreted with caution. Information on spontaneous tumor growth is lacking in most of these studies. Patients with different pretreatment modalities consisting of surgical interventions, embolization therapy, and/or chemotherapy have been included. In addition, the dose regimen, the type of IFN-α (rIFN-α2a, rIFN-α2b, human leukocyte IFN), and treatment time differed considerably between the studies. In these slow-growing tumors, changes might only be obvious after long treatment periods (up to 30 months). No randomized, prospective multicenter studies have been performed. Endpoint analysis, i.e., overall survival or time to progression, is given in about one third of the trials. Overall, results of these investigations delineate a consistent pattern of efficacy for IFN on symptom control.

In almost all patients (97%) a "flu-like" syndrome occurs in the first 5 days. Anorexia, weight loss (59%), and fatigue (51%) may adversely affect well-being. Bone marrow toxicity like anemia, leukocytopenia, and thrombocytopenia have been observed in 31, 7, and 18% of the patients, respectively, as well as hepatotoxicity (31%). These effects are dose dependent. Autoimmune reactions occur in 20% of the patients [46]. Rare side effects are depression, mental disturbances, and visual impairment.

In summary, IFN therapy is primarily given in patients with metastasized neuroendocrine tumors of the gut. The effect on symptoms of hormone hypersecretion is comparable to SSA, while the onset of response is delayed compared to SSA. IFN treatment will not cure the disease; however, it may be able to control tumor growth over extended periods, the smaller the tumor burden, the more so. Thus, IFN should be given rather early in the course of the disease. Side effects of IFN therapy are more pronounced than with SSA. Individualized doses allow a reasonable quality of life.

Table 5 Antiproliferative effects of interferon therapy

Interferon	Evaluable pats.	CR	PR	SD	PD	Author
IFN	14	–	–	9	5	[17]
IFN-α	20	–	–	15	5	[64]
IFN-α	15	–	3	NI	NI	[16]
rIFN-α	20	–	4	NI	NI	[44]
rIFN-α	12	–	2	9	1	[29]
rIFN-α2b	17	–	–	16	NI	[47]
rIFN-α2b	14	–	–	10	NI	[61]
rIFN-α2b	26		4	17	NI	[59]
rIFN-α2b	25	–	–	16	9	[28]
hIFN/ rIFN-α	111	–	16	74	21	[48]
Total	274		29/ 274	166/ 239	41/ 182	
Percent			11%	70%	23%	

CR Complete remission; *PR* partial remission; *SD* stable disease; *PD* progressive disease

Combination therapy: SSA plus IFN-α

The combination of SSA and IFN-α was used in an effort to enhance the antiproliferative effect of IFN therapy, to add the positive effect of SSA on hypersecretion syndromes, and to reduce the dose of IFN-α and, thus, the number of IFN-related side effects.

Earlier studies gave contradictory results showing either no additional or an increased antiproliferative effect with combination therapy. However, a recent, well-designed prospective multicenter study showed no advantage of combination therapy, neither on biochemical nor antiproliferative results, while the number of side effects increased [23]. Thus, combination therapy is not recommended as a standard treatment regimen.

In summary, biotherapy is preferentially indicated for the treatment of hormone hypersecretion syndromes in patients with neuroendocrine tumors. Antiproliferative effects are not convincing, but stabilization of the disease does occur in up to 50% of the patients with either SSA or IFN therapy. Combination treatment does not provide any additional effect and is not recommended.

Systemic chemotherapy

Chemotherapy is a palliative option in metastasizing neuroendocrine carcinomas. Streptozotocin (STZ), fluorouracil (5-FU), doxorubicin, dacarbazin (DTIC), etoposide, and cisplatin have been used. As the response rate to monotherapy has been low, most chemotherapeutic regimens for neuroendocrine tumors rely on combination therapy.

STZ is an alkylating nitrosurea compound. STZ enters the pancreatic β cell via the GLUT2 glucose transporter. However, the molecular mechanism of cytotoxicity is still unknown. STZ is effective in the treatment of neuroendocrine tumors of the pancreas. It is used in combination with either 5-FU or doxorubicin. STZ induces nausea and vomiting in up to 90% of patients, and glomerular and tubular dysfunctions occur in 20–75%. Bone marrow toxicity is low; thus, combinations with 5-FU or doxorubicin are possible.

5-FU is a pro-drug and needs to be metabolized for antineoplastic action. Its metabolites inhibit thymidilate synthetase, thus blocking DNA synthesis. In addition, RNA

synthesis is reduced. 5-FU preferentially inhibits proliferating cells, resulting in bone marrow toxicity and gastrointestinal side effects. Patients with coronary heart disease or cardiomyopathy are at risk for cardiotoxic side effects.

Doxorubicin is supposed to interact with DNA base pairs, and this may result in steric inhibition of DNA synthesis. Additional antineoplastic actions are possibly due to the formation of free radicals, an effect on tumor cell membranes and the inhibition of topoisomerase II activity. Myelosuppression is a dose-limiting side effect. Immediate, reversible, or irreversible cardiotoxicity has been observed. Nausea and vomiting are seen in up to 80% of the patients.

DTIC has cytostatic effects and inhibits the cell cycle. Additional effects are reduction of the DNA synthesis and alkylating effects. Therapy with dacarbazin can induce a rare veno-occlusive syndrome. However in most patients, toxicity is low, and the side effects experienced are mostly nausea and vomiting.

Cisplatin is an alkylating agent and, thus, interferes with DNA replication. Nausea and vomiting occur in up to 75% of the patients, myelosuppression is usually mild to moderate, with high-dose therapy. Nephrotoxicity is possible, peripheral neuropathy is common and is dose and duration dependent.

Etoposide, a podophyllotoxin derivative, is used in combination with cisplatin for poorly differentiated NET. Cytotoxicity is due to breaks of DNA strands. Etoposide interacts with topoisomerase II. The inhibition of the cell cycle during S and G2 phase is cytostatic. Side effects like nausea, vomiting and diarrhea, myelosuppression, and alopecia are common.

In neuroendocrine tumors of the pancreas, overall response rates of 17, 18–26, and 21% were obtained with monotherapy using STZ, 5-FU, and doxorubicin, respectively. Combination therapy for well-differentiated, neuroendocrine tumors of the pancreas, on the other hand, resulted in a median response of 36%. Median remission lasted 17 months, while median overall survival was almost 2 years (Table 6). The combination of STZ and 5-FU (N= 147) resulted in an objective response in 21% of the patients, with a median survival time from the start of therapy of less than 8 months. A recent randomized prospective trial (N=163) failed to confirm the suggested superiority of STZ and doxorubicin over STZ and 5-FU [62]. Objective remission was 16% for both arms, progression-free survival was 4.5 and 5.3 months, respectively. Overall survival was higher with STZ/5FU (24.3 vs 15.7 months, p<0.03), arguing for the less toxic approach with STZ/5-FU. Other combination schemes like dacarbazin, 5-FU and leucoverin (response rate 27%), dacarbazin, 5-FU and epirubicin (response rate 30%), lomustine and 5-FU (response rate 21%) were comparable. In a recent trial, 84 patients with pancreatic neuroendocrine tumors were treated with STZ, 5-FU, and doxorubicin [33]. This triple combination achieved a response rate of 39% and a median progression-free survival of 9.3 months, confirming earlier data in small investigations [57, 67].

In contrast, chemotherapy is less effective in neuroendocrine tumors of the small intestine. An overview over ten trials (1979–2005) indicates a median response rate of 25% and a median survival of 11 months (Table 7). Thus, in well-differentiated neuroendocrine tumors of the gut, chemotherapy is not a preferred option.

In contrast, in 18 patients with undifferentiated, anaplastic, neuroendocrine tumors (five tumors were of midgut/hindgut origin), 67% objective responses were obtained [43] with a median duration of remission of less than 8 months.

In interpreting these data, it has to be kept in mind that most studies comprise only a small number of patients; the patients usually are heterogeneous groups with respect to the localization of the tumor, total tumor burden, and pretreatment schemes.

In summary, combination therapy with STZ, 5-FU, with the possible addition of doxorubicin, are now standard treatment schedules in patients with well-differentiated neuroendocrine tumors of the pancreas. For neuroendocrine tumors of the small bowel, there is still no convincing evidence for improved survival with chemotherapy, and thus, other palliative options should be discussed. However, in patients with anaplastic neuroendocrine carcinomas, the

Table 6 Chemotherapy for well-differentiated neuroendocrine pancreatic tumors

Chemotherapy	*N*	Response (%)	PFS (month)	Median survival	Author
STZ	42	36	17	17	[40]
DTIC	42	33		19.3	[55]
STZ, 5-FU	42	63	17	26	[40]
STZ, Dox	25	36	22		[21]
STZ, Dox	16	6	18		[10]
STZ, Dox	3	30		18	[51]
STZ, Dox	36	69	18	26	[42]
STZ, 5-FU	33	45	14	18	[42]
CLZ, 5-FU	44	36	11		[8]
STZ, 5-FU, Dox	10	40		26	[67]
STZ, 5-FU, Dox	12	55	15	21	[57]
STZ, 5-FU, Dox	84	39	18	37	[33]
5-FU, Epi, DTIC	15	27	10		[7]
5-FU, Epi, DTIC	32	25	21	38	[6]
All	436	39	16.5	25	

STZ Streptozotocin; *DTIC* dacarbazin; *5-FU* 5-fluorouracil; *CLZ* chlorozotocin; *Dox* doxorubicin; *Epi* epirubicin

Table 7 Chemotherapy in well-differentiated neuroendocrine tumors of the small bowel

	N	Response (%)	Median survival	Author
Dox	81	21	11	[19]
STZ, 5-FU	80	22	15	[19]
STZ, 5-FU	43	33	NI	[39]
STZ, Dox	33	40	11	[24]
STZ, Dox	3	30	5	[51]
STZ, cyclophosphamide	47	26	NI	[39]
5FU, Dox, DTIC	20	10	5	[14]
5FU, CCNU	16	25	16	[32]
MTX, cyclophosphamide	16	0	NI	[43]
VP16, cisplatin	13	0	NI	[41]
	352	**21**		

Dox Doxorubicin; *STZ* streptozotocin; *5-FU* 5-fluorouracil; *DTIC* dacarbazin; *CCNU* lomustine; *MTX* methotrexate; *VP16* etoposide

combination of etoposide and cisplatin yielded a response rate of 67%, making this regimen a rewarding tool in undifferentiated neuroendocrine tumors of the intestine.

Novel agents

In tumor cells, the regulation and modulation of growth pathways is disturbed or mutated. This, in turn, leads to dysregulation of signalling pathways, accelerated cell proliferation, and growth. Targeted interaction with key components of these dysregulated signalling pathways may present a new option of tumor therapy. Possible targets are growth factors, growth factor receptors, angiogenetic molecules, and kinases involved in proliferation pathways [26]. Targeted therapy aims at different levels of these proliferation pathways like antibody-induced neutralization of vascular endothelial growth factor (VEGF) ligands or the epithelial growth factor receptor to prevent ligand–receptor interaction or direct inhibition of the receptor tyrosine kinase by small molecules. The best known examples of multi-kinase inhibitors are imatinib or sunitinib, with activity against kinases of platelet-derived growth factor receptor (PDGF-R), bcr-abl, c-kit and PDGF-R, VEGF-R, RET, and c-kit, respectively. RAD001 (everolimus) a rapamycin analogue, is an inhibitor of the mammalian target of rapamycin (mTOR). Inhibition of the protein kinase mTOR may reduce cell growth, increase apoptosis, and reduce metastatic spread. It may have synergistic effects with SSA, as the mTOR pathway is stimulated by IGF-1, which is inhibited by SSA.

These novel targeted therapies are now used in clinical trials for neuroendocrine tumors of foregut and midgut origin. Theoretical background is the known expression of PDGF-R and VEGF-R in neuroendocrine tumors. Results of in vitro investigations in neuroendocrine tumors cell models demonstrated effective inhibition of cell proliferation. Most of the following data are not yet published, but have been presented in abstract form.

Tyrosine kinase inhibitors

First clinical trials in neuroendocrine tumors with tyrosine kinase inhibitors demonstrated partial remission in 5–18%,

Table 8 Novel agents: tyrosine kinase inhibitors and anti-angiogenetic therapy in patients with gastroenteropancreatic neuroendocrine tumors

Drug	*N*		PR		SD		PD		Progression-free survival		Author
	P	SB	P	SB	P	SB	P	SB	P	SB	
Tyrosine kinase inhibitors											
Gefitinib	39	57	10%	5%	14%	32%			31% (6 months)	61% (6 months)	[25]
Imatinib	27		4%		63%					24 weeks (med)	[9]
Sunitinib	66	43	13%	2%	75%	93%			43 weeks (med)	42 weeks (med)	[34]
Everolimus+octreotide	13	18	18%	13%	55%	81%	15%	6%	65% (6 months)	65% (6 months)	[70]
Anti-angiogenic therapy											
Endostatin	40		0%		80%		20%		5.8 months (med)	7.6 months (med)	[35]
Bevacizumab+octreotide	22		18%		77%					96% (18 weeks)	[69]
Bevacizumab+ temozolamide	18	16	24%	0%	70%	92%	6%	8%			[36]
Thalidomide+ temozolamide[a]	11	15	25%		68%		7%		1-y 79%; 2-y 61%[b]		[37]

[a] Plus 3 pheochromocytomas
[b] Overall survival
P Pancreas; *SB* small bowel; *PR* partial remission; *SD* stable disease; *PD* progressive disease; *med* median

stable disease in 14–93% and progressive disease in 6–15% of the patients. Progression-free survival ranged from a median of 24 to 42 weeks or up to 60% at months 6. These first data indicate a slightly better result for patients with neuroendocrine tumors of the small bowel. Unfortunately, progressive disease was not a prerequisite for inclusions in all trials, and different tumor groups were included in the studies (Table 8). Side effects were tolerable in most of these studies, and the incidence of grade 4 toxicities was low.

In summary, the antiproliferative or stabilization effect of tyrosine kinase inhibitors is probable comparable to biotherapy. These molecules may have synergistic effects in combination with established treatment regimen. Thus, they may well widen the spectrum of effective therapeutic strategies in neuroendocrine tumor diseases.

Anti-angiogenic therapy

Anti-angiogenic therapy is directed vs the formation of new blood vessels. Tumor angiogenesis is regarded as a critical point in the development of growth and metastases. Thus, VEGF, an endothelial growth factor, VEGF-R, or the VEGF-R kinase are potential targets for anti-angiogenic therapy. Neuroendocrine tumors are highly vascularized, and VEGF expression is high. A correlation of the VEGF plasma concentration with tumor growth has been suggested. Therefore, anti-angiogenic therapy targets either the VEGF-R ligand, the VEGF-R, or VEGF-R kinase activity.

Endostatin or angiostatin act as inhibitors of the VEGF-R, antibodies like bevacizumab interfere with VEGF, and multikinase inhibitors like vatalanib (PTK/ZK) [63] inhibit angiogenesis. Thalidomide inhibits angiogenesis by interference with VEGF and basic fibroblast growth factor (bFGF) pathways and the extracellular matrix. These drugs reduce the formation of new vessels and act cytostatic. In contrast, substances directed vs existing tumor vasculature-like combrestatin induce cell necrosis and act cytotoxic. Due to their serious side effects, none of these vascular targeting therapies are clinically available at the time being.

With all the different anti-angiogenic strategies used so far, partial remission was seen in 0–25%, stabilization occurred in 68–92% and progressive disease in 2–20% (Table 8). Again, results are still preliminary, as most of these data are only published in abstract form. As progressive disease was no prerequisite for inclusion in some studies, the rate of stabilization as well as the intervals for progression-free survival or overall survival may be overestimated. Most therapy regimen were well tolerated. The combination of thalidomide and temozolamide, however, resulted in high bone marrow toxicity (~70%) with opportunistic infections in 10% of the patients with infectious complications [36].

In summary, molecular targeted therapies and angiogenesis inhibitors offer a promising approach to antiproliferation in neuroendocrine tumors. Results of ongoing trials will provide more stringent data due to more homogenous tumor groups, inclusion of patients with similar pre-therapeutic regimen, and demonstrated progressive disease. It is to be expected that these new drugs will preferentially be used in combination with standard treatment regimen to improve stabilization rates in well-differentiated neuroendocrine tumors. Long-term effectiveness of targeted therapy may well be overcome by the development of alternative intracellular signalling pathways, thus reducing therapeutic efficacy of the new regimen. On the other hand, depending on the expression pattern of targeted molecules in the tumor, pre-therapeutic patient selection may improve success rates in selected patients. Thus, classifying neuroendocrine tumors according to the expression of possible targeted molecules may be the future standard for effective therapeutic strategies.

Conflict of interest statement We declare that we have no conflict of interest.

References

1. Anthony L, Johnson D, Hande K, Shaff M, Winn, S, Krozely M, Oates J (1993) Somatostatin analogue phase I trials in neuroendocrine neoplasms. Acta Oncol 32:217–223
2. Aparicio T, Ducreux M, Baudin E, Sabourin JC, De Baere T, Mitry E, Schlumberger M, Rougier P (2001) Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. Eur J Cancer 37:1014–1019
3. Arnold R, Benning R, Neuhaus C, Rolwage M, Trautmann ME (1993a) Gastroenteropancreatic endocrine tumours: effect of Sandostatin on tumour growth. The German Sandostatin Study Group. Digestion 54(Suppl 1):72–75
4. Arnold R, Neuhaus C, Benning R, Schwerk WB, Trautmann ME, Joseph K, Bruns C (1993b) Somatostatin analog sandostatin and inhibition of tumor growth in patients with metastatic endocrine gastroenteropancreatic tumors. World J Surg 17:511–519
5. Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jurgense, R, Stein K, Schafer H, Bruns C, Dennler HJ (1996) Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut 38:430–438
6. Bajetta E, Rimassa L, Carnaghi C, Seregni E, Ferrari L, Di Bartolomeo M, Regalia E, Cassata A, Procopio G, Mariani L (1998) 5-Fluorouracil, dacarbazine, and epirubicin in the treatment of patients with neuroendocrine tumors. Cancer 83:372–378
7. Bajetta E, Ferrari L, Procopio G, Catena L, Ferrario E, Martinetti A, Di Bartolomeo M, Buzzoni R, Celio L, Vitali M, Beretta E, Seregni E, Bombardieri E (2002) Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumours. Ann Oncol 13:614–621
8. Bukowski RM, Tangen C, Lee R, Macdonald JS, Einstein AB Jr, Peterson R, Fleming TR (1992) Phase II trial of chlorozotocin and fluorouracil in islet cell carcinoma: a Southwest Oncology Group study. J Clin Oncol 10:1914–1918

9. Carr K, Yao J, Rashid A, Yeung SC, Szklaruk J, Baker J, Vauthey JN, Curley S, Ellis L, Ajani JA (2004) A phase II trial of imatinib in patients with advanced carcinoid tumor. J Clin Oncol, ASCO Annual Meeting Proceedings (Post-Meeting Edition), 22(14S):4124
10. Cheng PN, Saltz LB (1999) Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer 86:944–948
11. Dasgupta P (2004) Somatostatin analogues: multiple roles in cellular proliferation, neoplasia, and angiogenesis. Pharmacol Ther 102:61–85
12. De Herder WW, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falconi M, Kwekkeboom DJ, Oberg K, Eriksson B, Wiedenmann B, Rindi G, O'Toole D, Ferone D (2006) Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology 84:183–188
13. Detjen KM, Welzel M, Farwig K, Brembeck FH, Kaiser A, Riecken EO, Wiedenmann B, Rosewicz S (2000) Molecular mechanism of interferon alfa-mediated growth inhibition in human neuroendocrine tumor cells. Gastroenterology 118:735–748
14. Di Bartolomeo M, Bajetta E, Bochicchio AM, Carnaghi C, Somma L, Mazzaferro V, Visini M, Gebbia V, Tumolo S, Ballatore P (1995) A phase II trial of dacarbazine, fluorouracil and epirubicin in patients with neuroendocrine tumours. A study by the Italian Trials in Medical Oncology (I.T.M.O.) Group. Ann Oncol 6:77–79
15. Di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, Zilembo N, Di Leo A (1996) Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. Cancer 77:402–408
16. Dirix LY, Vermeulen PB, Fierens H, De Schepper B, Corthouts B, Van Oosterom AT (1996) Long-term results of continuous treatment with recombinant interferon-alpha in patients with metastatic carcinoid tumors—an antiangiogenic effect? Anticancer Drugs 7:175–181
17. Doberauer C, Mengelkoch B, Kloke O, Wandl U, Niederle N (1991) Treatment of metastatic carcinoid tumors and the carcinoid syndrome with recombinant interferon alpha. Acta Oncol 30:603–605
18. Ducreux M, Ruszniewski P, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Hammel P, Rougier P (2000) The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. Am J Gastroenterol 95:3276–3281
19. Engstrom PF, Lavin PT, Moerte, CG, Folsch E, Douglass HO Jr (1984) Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol 2:1255–1259
20. Eriksson B, Skogseid B, Lundqvist G, Wide L, Wilander E, Oberg K (1990) Medical treatment and long-term survival in a prospective study of 84 patients with endocrine pancreatic tumors. Cancer 65:1883–1890
21. Eriksson B, Renstrup J, Imam H, Oberg K (1997) High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. Ann Oncol 8:1041–1044
22. Falconi M, Plockinger U, Kwekkeboom DJ, Manfredi R, Korner M, Kvols L, Pape UF., Ricke J, Goretzki PE, Wildi S, Steinmuller T, Oberg K, Scoazec JY (2006) Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 84:196–211
23. Faiss S, Pape UF., Bohmig M, Dorffel Y, Mansmann U, Golder W, Riecken EO, Wiedenmann B (2003) Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 21:2689–2696
24. Frame J, Kelsen D, Kemeny N, Cheng E, Niedzwiecki D, Heelan R, Lippermann R (1988) A phase II trial of streptozotocin and adriamycin in advanced APUD tumors. Am J Clin Oncol 11:490–495
25. Hobday TJ, Holen K, Donehower R, Camoriano J, Kim G, Picus J, Philip P, Lloyd R, Mahoney M, Erlichman C (2006) A phase II trial of gefitinib in patients (pts) with progressive metastatic neuroendocrine tumors (NET): a phase II consortium (P2C) study. J Clin Oncol, ASCO Annual Meeting Proceedings Part I, 24 (18S):4043
26. Hobday TJ, Rubin J, Goldberg R, Erlichman C, Lloyd R (2003) Molecular markers in metastatic gastrointestinal neuroendocrine tumors. Proc Am Soc Clin Oncol 22:269
27. Hofland LJ, Lamberts SW (2003) The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr Rev 24:28–47
28. Jacobsen MB, Hanssen LE, Kolmannskog F, Schrumpf E, Vatn MH, Bergan A (1995) Interferon-alpha 2b, with or without prior hepatic artery embolization: clinical response and survival in midgut carcinoid patients. The Norwegian carcinoid study. Scand J Gastroenterol 30:789–796
29. Janson ET, Ronnblom L, Ahlstrom H, Grander D, Alm G, Einhorn S, Oberg K (1992) Treatment with alpha-interferon versus alpha-interferon in combination with streptozocin and doxorubicin in patients with malignant carcinoid tumors: a randomized trial. Ann Oncol 3:635–638
30. Jensen RT, Niederle B, Mitry E, Ramage JK, Steinmuller T, Lewington V, Scarpa A, Sundin A, Perren A, Gross D, O'Connor JM, Pauwels S, Kloppel G (2006a) Gastrinoma (duodenal and pancreatic). Neuroendocrinology 84:173–182
31. Jensen RT, Rindi G, Arnold R, Lopes JM, Brandi ML, Bechstein WO, Christ E, Taal BG, Knigge U, Ahlman H, Kwekkeboom DJ, O'Toole D (2006b) Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). Neuroendocrinology 84:165–172
32. Kaltsas GA, Mukherjee JJ, Isidori A, Kola B, Plowman PN, Monson JP, Grossman AB, Besser GM (2002) Treatment of advanced neuroendocrine tumours using combination chemotherapy with lomustine and 5-fluorouracil. Clin Endocrinol (Oxf) 57:169–183
33. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC (2004) Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 22:4762–4771
34. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Picus J, Ryan DP, Bergsland E, Stuart K, Baum CM, Fuchs Cs (2005) Results of a phase II study with sunitinib malate (SU11248) in patients with advanced neuroendocrine tumours (NETs). Eur J Cancer 3:406
35. Kulke M, Bergsland E, Ryan D, Enzinger P, Lynch T, Zhu A, Meyerhardt J, Heymach J, Fogler W, Sidor C, Michelini A, Kinsella K, Venook A, Fuchs C (2006) Phase II study of recombinant human endostatin in patients with advanced neuroendocrine tumors. J Clin Oncol 24:3555–3561
36. Kulke MH, Stuart K, Earle C, Bhargava P, Clark J, Enzinger PC, Meyerhardt J, Attawia M, Lawrence C, Fuchs C (2006a) A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors. J Clin Oncol, ASCO Annual Meeting Proceedings Part I, 24(18S):4044
37. Kulke MH, Stuart K, Enzinger Pc, Ryan Dp, Clark Jw, Muzikansky A, Vincitore M, Michelini A, Fuchs Cs (2006b) Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 24:401–406
38. Lamberts SW, Krenning EP, Reubi JC (1991) The role of somatostatin and its analogs in the diagnosis and treatment of tumors. Endocr Rev 12:450–482

39. Moertel CG, Hanley JA (1979) Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials 2:327–334
40. Moertel CG, Hanley JA, Johnson LA (1980) Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 303:1189–1194
41. Moertel CG, O'Connell MJ, Reitemeier RJ, Rubin J (1984) Evaluation of combined cyclophosphamide and methotrexate therapy in the treatment of metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Treat Rep 68:665–667
42. Moertel CG, Rubin J, Kvols LK (1989) Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. J Clin Oncol 7:865–868
43. Moertel CG, Kvols LK, O'Connell MJ, Rubin J (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 68:227–232
44. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D (1992) Streptozocin–doxorubicin, streptozocin–fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 326:519–523
45. Oberg K (1992) The action of interferon alpha on human carcinoid tumours. Semin Cancer Biol 3:35–41
46. Oberg K (1994) Endocrine tumors of the gastrointestinal tract: systemic treatment. Anticancer Drugs 5:503–519
47. Oberg K, Eriksson B (1989) Medical treatment of neuroendocrine gut and pancreatic tumors. Acta Oncol 28:425–431
48. Oberg K, Eriksson B (1991) The role of interferons in the management of carcinoid tumours. Br J Haematol 79(suppl 1):74–77
49. O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A., De Herder WW, Hyrdel R, Nikou G., Krenning E, Vullierme MP, Caplin M, Jensen R, Eriksson B (2006) Rare functioning pancreatic endocrine tumors. Neuroendocrinology 84:189–195
50. Panzuto F, Di Fonzo M, Iannicelli E, Sciuto R, Maini CL, Capurso G, Milione M, Cattaruzza MS, Falconi M, David V, Ziparo V, Pederzoli P, Bordi C, Fave GD (2006) Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma. Ann Oncol 17:461–466
51. Pavel ME, Baum U, Hahn EG, Hensen J (2005) Doxorubicin and streptozotocin after failed biotherapy of neuroendocrine tumors. Int J Gastrointest Cancer 35:179–185
52. Plöckinger U, Perez-Canto A, Emde C, Liehr RM, Hopfenmuller W, Quabbe HJ (1998) Effect of the somatostatin analog octreotide on gastric mucosal function and histology during 3 months of preoperative treatment in patients with acromegaly. Eur J Endocrinol 139:387–394
53. Plöckinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, De Herder WW, Goede A, Caplin M, Oberg K, Reubi JC, Nilsson O, Delle Fave G, Ruszniewski P, Ahlman H, Wiedenmann B (2004) Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 80:394–424
54. Plöckinger U (2007) Diagnosis and treatment of gastric neuroendocrine tumours. In: Wiedenmann B, Niederle B (eds) Hypergastrinemia—diagnosis and treatment. Wien Klin Wochenschr (in press)
55. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG (2001) Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 12:1139–1143
56. Ricci S, Antonuzzo A, Galli L, Orlandini C, Ferdeghini M, Boni G, Roncella M, Mosca F, Conte PF (2000) Long-acting depot lanreotide in the treatment of patients with advanced neuroendocrine tumors. Am J Clin Oncol 23:412–415
57. Rivera E, Ajani JA (1998) Doxorubicin, streptozocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. Am J Clin Oncol 21:36–38
58. Ruszniewski P, Delle Fave G, Cadiot G, Komminoth P, Chung D, Kos-Kudla B, Kianmanesh R, Hochhauser D, Arnold R, Ahlman H, Pauwels S, Kwekkeboom DJ, Rindi G (2006) Well-differentiated gastric tumors/carcinomas. Neuroendocrinology 84:158–164
59. Schober C, Schmoll E, Schmoll HJ, Poliwoda H, Schuppert F, Stahl M, Bokemeyer C, Wilke H, Weiss J (1992) Antitumour effect and symptomatic control with interferon alpha 2b in patients with endocrine active tumours. Eur J Cancer 28A:1664–1666
60. Shah T, Caplin M (2005) Endocrine tumours of the gastrointestinal tract. Biotherapy for metastatic endocrine tumours. Best Pract Res Clin Gastroenterol 19:617–636
61. Smith DB, Scarffe JH, Wagstaff J, Johnston RJ (1987) Phase II trial of rDNA alfa 2b interferon in patients with malignant carcinoid tumor. Cancer Treat Rep 71:1265–1266
62. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG (2005) Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 23:4897–4904
63. Thomas Al, Morgan B, Horsfield MA, Higginson A, Kay A, Lee L, Masson E, Puccio-Pick M, Laurent D, Steward WP (2005) Phase I study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of PTK787/ZK 222584 administered twice daily in patients with advanced cancer. J Clin Oncol 23:4162–4171
64. Tiensuu Janson EM, Ahlstrom H, Andersson T, Oberg KE (1992) Octreotide and interferon alfa: a new combination for the treatment of malignant carcinoid tumours. Eur J Cancer 28A:1647–1650
65. Tomassetti P, Migliori M, Gullo L (1998) Slow-release lanreotide treatment in endocrine gastrointestinal tumors. Am J Gastroenterol 93:1468–1471
66. Tomassetti P, Migliori M, Corinaldesi R, Gullo L (2000) Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. Aliment Pharmacol Ther 14:557–560
67. Von Schrenck T, Howard JM, Doppman JL, Norton JA, Maton PN, Smith FP, Vinayek R, Frucht H, Wank SA, Gardner JD (1988) Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology 94:1326–1334
68. Wymenga AN, Eriksson B, Salmela PI, Jacobsen MB, Van Cutsem EJ, Fiasse RH, Valimaki MJ, Renstrup J, De Vries EG, Oberg KE (1999) Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. J Clin Oncol 17:1111
69. Yao J, Ng C, Hoff PM, Phan A, Hess K, Chen H, Wang X, Abbruzzese J, Ajani JA (2005) Improved progression free survival (PFS), and rapid, sustained decrease in tumor perfusion among patients with advanced carcinoid treated with bevacizumab. J Clin Oncol, ASCO Annual Meeting Proceedings Part I, 23(6S):4007
70. Yao J, Phan A, Chang D, Jacobs C, Mares J, Rashid A, Meric-Bernstam F (2006) Phase II study of RAD001 (everolimus) and depot octreotide (sandostatin LAR) in patients with advanced low grade neuroendocrine carcinoma (LGNET). J Clin Oncol, ASCO Annual Meeting Proceedings Part I, 24(18S):4042