Rebecca Kinkead. *Jumpin' on the Bed* (detail), 2010. Oil on canvas, 48″ × 48″.

Results from clinical trials show promise in expanding treatment options for metastatic gastroenteropancreatic neuroendocrine tumors.

A Review of Systemic and Liver-Directed Therapies for Metastatic Neuroendocrine Tumors of the Gastroenteropancreatic Tract

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Background: *Treatment options for metastatic gastroenteropancreatic neuroendocrine tumors (NETs) have evolved in recent years. The somatostatin analogs octreotide and lanreotide have long been used for management of symptoms such as flushing and diarrhea associated with hormonally active NETs. New evidence demonstrates that these agents can also inhibit tumor growth. Other novel agents targeting the VEGF and mTOR pathways have recently been investigated in multicenter phase III studies.*

Methods: *The authors review the recent literature on treatments for metastatic gastroenteropancreatic NETs and summarize new therapeutic developments.*

Results: *Novel agents targeting somatostatin receptors and the VEGF and mTOR pathways are capable of significantly prolonging progression-free survival in certain NET subtypes. New temozolomide-based chemotherapy regimens have demonstrated considerable activity in pancreatic NETs. Liver-targeted therapies, including surgical resection, radiofrequency ablation, and hepatic artery embolization, are effective options for patients whose metastases are predominantly confined to the liver. Embolization of ^{90}Y-embedded spheres (radioembolization) represents a novel approach to managing liver metastases.*

Conclusions: *Treatment options are expanding rapidly for patients with metastatic gastroenteropancreatic NETs, driven largely by randomized, collaborative clinical trials. Future clinical trials should compare the efficacy of emerging therapies and evaluate combination vs sequential approaches.*

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Submitted June 2, 2010; accepted September 16, 2010.

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Dr Kvols is a consultant for and receives honoraria from Novartis, AG. The other authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

The authors have disclosed that this article discusses unlabeled/unapproved uses of the drugs everolimus, bevacizumab, sunitinib, temozolomide, capecitabine, 5-fluorouracil, dacarbazine, cisplatin, etoposide, interferon alfa, ^{177}lutetium-octreotate, and yttrium-octreotide for the treatment of metastatic neuroendocrine tumors.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms composed of carcinoid tumors and pancreatic NETs. The majority are characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones and other vasoactive substances, giving rise to diverse clinical syndromes. Histologically, carcinoid tumors arise from the endocrine (enterochromaffin) cells of the gastrointestinal tract and airways.

Carcinoid tumors have distinct features depending on their site of origin. In the 1960s, Williams et al[1] classified carcinoid tumors based on embryologic derivation, distinguishing between foregut (bronchial, stomach,

duodenal), midgut (jejunal, ileal, cecal, appendiceal), and hindgut (distal colon and rectal). As a rule, metastatic midgut carcinoid tumors produce serotonin and other vasoactive substances that give rise to the typical carcinoid syndrome.[2] This syndrome manifests primarily as diarrhea and flushing, a vasomotor phenomenon that causes redness and warmth in the face and upper torso.[3] Carcinoid heart disease, characterized by fibrosis of the tricuspid and pulmonic heart valves, can also occur in patients with severe and prolonged elevations of circulating serotonin.[4] In contrast, hindgut carcinoid tumors are rarely, if ever, associated with a hormonal syndrome.

Tumor growth rates also correlate with the site of origin. In the metastatic setting, midgut carcinoid tumors tend to behave in an indolent fashion, whereas NETs originating in the foregut or hindgut regions tend to behave more aggressively once they have metastasized.

Pancreatic neuroendocrine tumors (PNETs) arise from the islets of Langerhans. These heterogeneous neoplasms can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP). The annual incidence of PNETs is approximately 1 per 100,000.[5] In contemporary studies, most PNETs are unassociated with a hormonal syndrome and are termed *nonfunctioning*.[6,7] Among the hormone-producing tumors, insulinomas tend to behave in a benign fashion and have a malignancy rate of only 10%. The majority of gastrinomas, VIPomas, glucagonomas, and nonfunctioning tumors are metastatic at presentation.

Treatment options for metastatic NETs have evolved in recent years. The somatostatin analogs (SSAs) octreotide and lanreotide were initially developed to palliate hormonal symptoms such as flushing and diarrhea caused by the carcinoid syndrome. More recently, accumulating data have supported their role as antiproliferative agents, capable of stabilizing tumor growth in patients with metastatic neuroendocrine malignancies.[8] Emerging evidence supports the use of other targeted agents, although none yet is considered standard of care. Sunitinib, a multitargeted tyrosine kinase receptor inhibitor, has recently been demonstrated to prolong progression-free survival (PFS) in patients with metastatic PNETs.[9] Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), has shown promise in several phase II studies.[10,11] In a recent randomized, placebo-controlled phase III trial, everolimus demonstrated prolongation of progression-free survival in patients with advanced PNETs.[12] Bevacizumab, an inhibitor of circulating vascular endothelial growth factor (VEGF), is also being tested in phase III studies based on encouraging phase II evidence.[13] While cytotoxic chemotherapy appears to produce high response rates in metastatic PNETs,[14-16] responses in carcinoid tumors have been discouraging.

Hepatic-directed therapies are appropriate for patients whose tumors are predominantly metastatic to the liver. Options for patients with limited metastases include resection or ablative techniques such as radiofrequency ablation. Modern surgical techniques now enable tumor cytoreduction in patients with multiple bilobar metastases. For patients with diffuse hepatic tumors, intra-arterial embolization techniques such as hepatic artery embolization, chemoembolation, or radioembolization are often utilized.

Tumor differentiation and grade are important predictive and prognostic factors. While often used interchangeably, differentiation and grade are not identical terms: differentiation refers to the similarity between the tumor histology and tissue of origin, whereas grade is calculated based on markers of proliferation such as mitotic rate and Ki-67 proliferative index. In general, poorly differentiated (high-grade) tumors are characterized by an elevated mitotic rate (> 10 to 20 mitoses per 10 high-powered fields), a high Ki-67 proliferative index (typically > 20%), extensive necrosis, and pleomorphism.[17,18] These

Table 1. — Summary of Clinical Trials Evaluating the Antisecretory Effect of Somatostatin

Study (yr)	Disease	No. of Patients	Drug	Symptom Response	Biochemical Response
Kvols[28] (1986)	Carcinoid	25	Octreotide 450 mg/d	88%	72%
di Bartolomeo[29] (1996)	Carcinoid PET	31 12	Octreotide 1500-3000 mcg/d	73%	77%
Maton[30] (1989)	VIPoma Insulinoma Glucagonoma	7 6 15	Octreotide	100% 100% 83%	–
Rubin[31] (1999)	Carcinoid	93	Octreotide vs depot-octreotide 10-30 mg	58% vs 66%	–
O'Toole[32] (2000)	Carcinoid	33	Octreotide 300-600 mcg/d vs lanreotide 30 mg	68% vs 54%	50% vs 58%

aggressive tumors are associated with a substantially worse prognosis than well-differentiated NETs despite their increased sensitivity to cytotoxic chemotherapy.[19] Most targeted agents have not been formally tested in poorly differentiated tumors.

The overall survival of patients with metastatic gastroenteropancreatic NETs appears to have improved substantially in the past three decades.[6,20,21] One potential factor may be the expansion of therapeutic options, particularly the widespread use of SSAs. This review summarizes the standard and investigational agents used for treatment of these rare and challenging malignancies.

Somatostatin Analogs

SSAs have had a profound impact on patients with the carcinoid syndrome and other hormonal symptoms associated with functioning NETs.[3] The development of SSAs arose from the recognition that native human somatostatin functions as an inhibitor of endocrine activity.[22-24] For example, in the digestive tract, it decreases portal blood flow, reduces gastrointestinal secretion, inhibits peristalsis, and downregulates the secretion of other gastrointestinal hormones.[25] Somatostatin exerts its effects through interaction with five somatostatin receptors ($ssts_{1-5}$) belonging to a family of G-protein coupled receptors.[26] The clinical use of native human somatostatin is impeded by its short half-life of approximately 2 minutes.[27] Consequently, synthetic SSAs have been designed to increase molecular stability by eliminating enzymatic cleavage sites while retaining binding affinity to somatostatin receptors.

The SSAs currently used in clinical practice are octreotide and lanreotide, cyclic peptides with half-lives of approximately 2 hours.[28] Both analogs bind avidly to sst_2 and moderately to sst_5. In a landmark study, octreotide was tested in 25 patients with malignant carcinoid syndrome. Flushing and diarrhea were substantially palliated in 22 patients (88%), and major reductions in urine 5-HIAA were reported in 18 cases (72%).[28] Numerous subsequent trials have validated the antisecretory effects of octreotide and lanreotide in patients with the carcinoid syndrome as well as other neuroendocrine hormonal syndromes, notably the VIPoma and glucagonoma syndromes (Table 1).[28-32] Both octreotide and lanreotide are exceptionally well-tolerated agents. Side effects, which are generally mild, include nausea, bloating, and steatorrhea. Long-term use can result in cholelithiasis caused by inhibition of gallbladder contractility.[33]

Octreotide was originally developed as an immediate-release subcutaneous formulation and tested at doses of 100 to 500 mcg administered two to three times daily. During the past decade, a long-acting repeatable (LAR) depot formulation of octreotide (Sandostatin LAR) has been available, which enables monthly intramuscular dosing.[31] The initial clinical trial of octreotide LAR for treatment of the carcinoid syndrome investigated doses of 10, 20, and 30 mg every 4 weeks. In clinical practice, higher doses of up to 60 mg are frequently administered to patients who develop refractory hormonal symptoms.[34] Doses exceeding 60 mg are unlikely to be of additional palliative benefit, given saturation of somatostatin receptors.[35] Patients who experience exacerbation of symp-

Table 2. — Summary of Nonrandomized Clinical Trials Evaluating the Antiproliferative Effect of Somatostatin Analogs

Analog	Study (yr)	No. of Patients	Complete/Partial Response	Stable Disease	Progressive Disease
Patients With Documented Tumor Progression					
Lanreotide	Faiss[50] (2003)	22	1	7	14
Lanreotide	Aparicio[51] (2001)	35	1	20	14
Octreotide	Arnold[52] (1996)	52	0	19	33
Octreotide	Saltz[46] (1993)	34	0	17	17
Octreotide	di Bartolomeo[29] (1996)	58	2	27	29
		201	**4 (1%)**	**90 (45%)**	**107 (53%)**
Patients Without Documented Tumor Progression					
Lanreotide	Wymenga[49] (1999)	31	2	25	4
Lanreotide	Ducreux[53] (2000)	39	2	21	16
Lanreotide	Eriksson[47] (1997)	19	1	12	6
Lanreotide	Tomassetti[55] (1998)	18	0	14	4
Octreotide	Tomassetti[48] (2000)	16	0	14	2
Octreotide	Ricci[54] (2000)	15	1	6	8
		138	**6 (4%)**	**92 (67%)**	**40 (29%)**

toms toward the end of each treatment cycle may benefit from more frequent drug administration (every 2 to 3 weeks).[34] A long-acting lanreotide formulation (Somatuline autogel) is also available, and it is administered as a deep subcutaneous injection at doses ranging from 90 to 120 mg every 4 weeks.[36]

Pasireotide, a novel SSA, is currently in clinical development. It binds avidly to four of the five somatostatin receptors (sst_1, sst_2, sst_3, sst_5). An open-label trial evaluated the activity of subcutaneous pasireotide in patients with carcinoid syndrome whose symptoms were inadequately controlled on octreotide.[37] Preliminary data indicated activity in this refractory population. A randomized clinical study is currently evaluating the ability of a depot formulation of pasireotide (LAR) to palliate flushing and diarrhea in patients who are refractory to octreotide.

The Antiproliferative Effects of SSAs

SSAs were initially developed for control of hormonal syndromes associated with NETs. In recent years, increasing data have supported the hypothesis that they can also function as antineoplastic agents capable of inhibiting tumor growth.[8] In vitro evidence demonstrates that SSAs can inhibit tumor growth through direct and indirect mechanisms. Direct mechanisms involve interaction with somatostatin receptors on tumor cells. It appears that all somatostatin receptor subtypes can mediate inhibition of cellular proliferation, whereas specific receptors can also stimulate cellular apoptosis.[38-40] Although the precise signaling transduction pathways have not been fully elucidated, the primary steps appear to involve activation of phosphotyrosine phosphatases (PTPs)[41] and inhibition of adenylate cyclase.[42] Indirect inhibitory effects on tumor growth occur through suppression of circulating growth factors like VEGF, insulin-like growth factor (IGF), and growth hormone.[43-45]

Until recently, evidence of the antiproliferative effects of SSAs derived from single-arm phase II trials documenting a relatively high rate of disease stabilization among patients with NETs treated with octreotide or lanreotide (Table 2).[29,46-55] Higher-level evidence supporting the antiproliferative effect of octreotide emerged recently after publication of the PROMID study, a randomized phase III trial comparing octreotide LAR 30 mg vs placebo in 85 patients with metastatic midgut NETs.[56] The study reported a clinically and statistically significant prolongation in median time to progression from 6 months in the placebo arm to 14.3 months in the octreotide LAR 30 mg arm. (P = .000072) (Figure). Serious adverse events were evenly balanced (11 patients in the octreotide LAR group and 10 patients in the placebo arm). The small number of deaths in both treatment arms and the high rate of crossover precluded any meaningful analysis of overall survival differences. A randomized trial evaluating lanreotide vs placebo in nonfunctioning gastroenteropancreatic NETs is ongoing.

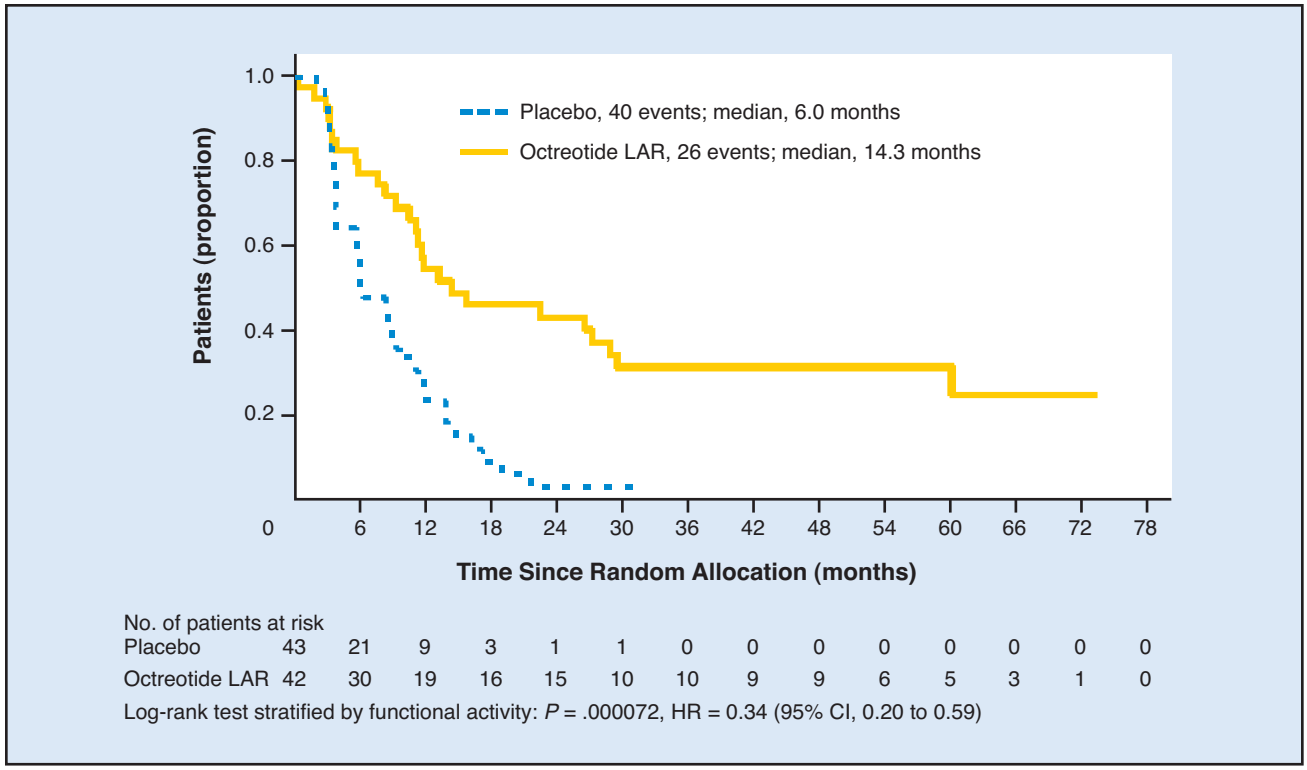

Figure. — Conservative intent-to-treat analysis of time to progression or tumor-related death. From Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27(28):4656-4663. Reprinted with permission.

Interferon Alfa

Interferons can exert antitumor effects through a variety of mechanisms, including stimulation of T cells, induction of cell cycle arrest in the G_1 and G_0 phases, and inhibition of angiogenesis.[57] In NETs, interferons can also induce upregulation of somatostatin receptors.[58] Interferon alfa (IFN-α), also known as leukocyte IFN, has been the type of interferon primarily studied in NETs. Early trials of IFN-α in hormonally functional NETs took place prior to the introduction of SSAs and reported significant palliation of hormonal symptoms such as flushing and diarrhea along with reductions of tumor markers in over 50% of patients.[59-61] Objective tumor response rates have generally been in the 4% to 10% range, with high rates of tumor stabilization.

With the development of SSAs, in vitro studies suggested synergism between IFN-α and SSAs, leading several investigators to evaluate the combination of the two therapies. One trial of patients with carcinoid syndrome who had become refractory to octreotide reported symptomatic improvement in 49% of patients after the addition of IFN-α.[62] Another study reported a 67% rate of disease stability in patients with progressive NETs treated with a similar combination.[63]

Three randomized clinical trials have investigated SSAs alone vs in combination with IFN-α. In one multicenter study of 68 patients evaluating subcutaneous octreotide alone or in combination with IFN-α at 3 million units 5 times per week, the 5-year survival rate was prolonged in the combination group (57% vs 37%) but not in a statistically significant fashion (P = .13).[64] Another three-arm trial compared subcutaneous lanreotide to IFN-α 5 million units 3 times per week alone or in combination. Objective response rates were rare (≤ 7%) in all three arms, and tumor progression rates were nearly identical.[65] A third randomized study of 109 patients compared subcutaneous octreotide alone or in combination with IFN-α at 4.5 million units 3 times per week. Survival in the combined arm was prolonged (51 vs 35 months) but did not achieve statistical significance (P = .38). Response rates in both arms were < 6%.[66]

The underpowered nature of the above-mentioned randomized studies precludes any definitive conclusions regarding the effects of IFN-α on overall survival. Moreover, an optimal dosing regimen has never been established. Enthusiasm for IFN-α therapy is tempered by potential side effects such as fevers, chills, myalgias, depression, and myelosuppression. However, toxicities have been relatively tolerable at the dose ranges studied in NETs.

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a conserved serine/threonine kinase that regulates cell growth, proliferation, and metabolism in response to environmental factors.[67] In addition, it appears to play a role in the control of apoptotic cell death. The mTOR enzyme lies downstream of the PI3K/AKT pathway and is upregulated in a variety of malignancies in response to stimulation by growth factors and cytokines. The tuberous sclerosis complex (TSC1, TSC2) is an endogenous inhibitor of mTOR. The importance of mTOR in neuroendocrine cancers is highlighted by the fact that patients with germline mutations of TSC2 are prone to develop PNETs.[68]

The mTOR inhibitors temsirolimus and everolimus have both been studied in NETs. In a phase II study of metastatic NETs, temsirolimus was associated with an intent-to-treat response rate of 5.6% with a median time to progression of 6 months.[69] Everolimus was associated with a more promising response rate of 20% and a median PFS of 15 months in a phase II study of 60 patient.[10] In a follow-up multicenter study of 160 patients with advanced, progressive PNETs (RADIANT 1), patients were evaluated in two strata: everolimus monotherapy (n = 115) or everolimus plus octreotide (n = 45).[11] Response rates and median PFS were 9% and 9.7 months, respectively in the monotherapy arm vs 4% and 16.7 months in the combined therapy arm.

Currently, two large phase III studies comparing everolimus 10 mg daily vs placebo in metastatic functional carcinoid tumors (RADIANT 2) and pancreatic NETs (RADIANT 3) have completed accrual. The RADIANT 3 trial demonstrated a statistically significant improvement in PFS from 4 months on the placebo arm to 11 months in the active treatment arm.[12] The RADIANT 2 trial demonstrated an improvement in PFS from 11 months on the placebo arm to 16 months on the active treatment arm. On central radiologic review, the statistical significance of this trial was borderline (P = .026).[70]

Angiogenesis Inhibitors

Neuroendocrine tumors are highly vascular and frequently overexpress the VEGF ligand and receptor (VEGFR).[71] Moreover, elevated circulating VEGF has been associated with tumor progression in NETs. Consequently, inhibition of the VEGF pathway has been a promising treatment target.

Bevacizumab is a monoclonal antibody to circulating VEGF. In a randomized phase II trial, 44 patients with metastatic carcinoid tumors were randomly assigned to treatment with bevacizumab or pegylated IFN-α2b (PEG-IFN) for 18 weeks after which they received both agents in combination.[13] At the week-18 time point, the PFS rate was 95% on the bevacizumab arm vs 68% on the PEG-IFN arm. Moreover, the objective radiographic response rate in the bevacizumab arm was 18%, indicating a high degree of clinical activity. An ongoing phase III study led by the Southwest Oncology Group (SWOG) is comparing bevacizumab to IFN-α in patients with metastatic carcinoid tumors, with a primary endpoint of PFS.

The tyrosine kinase receptor inhibitor sunitinib is an inhibitor of VEGFR-1, -2, and -3, as well as platelet-derived

Table 3. — Summary of Studies Evaluating Chemotherapy in PNETs

Regimen	No. of Patients	Author (yr)	Complete/Partial Response
STZ + 5-FU vs STZ	88	Moertel[73] (1980)	63% vs 36%
STZ + doxorubicin vs STZ + 5-FU	125	Moertel[15] (1992)	69% vs 45%
Dacarbazine	50	Ramanathan[74] (2001)	34%
STZ + 5-FU + doxorubicin	84	Kouvaraki[14] (2004)	39%
TMZ + thalidomide	11*	Kulke[75] (2006)	45%*
TMZ + capecitabine	30	Strosberg[16] (2010)	70%

* Out of 29 patients with metastatic NETs, 11 were pancreatic in origin. STZ = streptozocin, 5-FU = 5-fluorouracil, TMZ = temozolomide.

growth factor (PDGF), KIT, and FLT3. In a two-cohort phase II study of 109 patients, the objective response rates associated with sunitinib monotherapy were 16.7% and 2.4% in PNETs and carcinoid NETs, respectively.[72] Based on the relatively high response rates in PNETs, a multinational phase III study was launched comparing sunitinib (37.5 mg daily) to placebo.[9] The study, which was discontinued on interim analysis after enrollment of 171 patients, demonstrated a median PFS of 11.1 months on the sunitinib arm vs 5.5 months on the placebo arm. The objective response rate associated with sunitinib was 9.3%.

Cytotoxic Chemotherapy

The sensitivity of NETs to cytotoxic chemotherapy appears to correlate with primary tumor location and tumor grade. PNETs have long been effectively treated with the nitrosurea streptozocin (STZ). Two randomized trials conducted by the Eastern Cooperative Oncology Group (ECOG) in the 1970s and 1980s reported response rates of 63% with STZ plus 5-fluorouracil (5-FU) vs 36% with STZ monotherapy[73] and response rates of 69% with the combination of STZ and doxorubicin vs 45% with STZ and 5-FU[14] (Table 3).[14-16,73-75] These high response rates have been subsequently questioned due to the partial reliance on nonradiographic response criteria. A more recent retrospective study investigating the combination of STZ, 5-FU, and doxorubicin in PNETs reported a response rate of 39% using objective radiographic criteria and a median response duration of 9.3 months.[14] Dacarbazine (DTIC) is another active agent in PNETs, with a response rate of 34% in one phase II trial.[74]

The clinical use of STZ and dacarbazine has been limited by toxicity concerns. In recent years, the oral alkylating agent temozolomide has emerged as an active agent in PNETs. Like dacarbazine, temozolomide is converted to the active alkylator MTIC that induces DNA methylation at the O^6 position of guanine. A phase II study investigating the combination of temozolomide and thalidomide demonstrated an objective response rate of 45% in the PNET subset of patients.[75] A recent retrospective study of temozolomide combined with capecitabine in 30 chemo-naive PNET patients reported an objective radiographic response rate of 70% and median PFS of 18 months.[16] Side effects were relatively tolerable, with a grade 3/4 adverse event rate of only 12%.

Low-grade carcinoid tumors appear significantly more resistant to the effects of cytotoxic chemotherapy. Contemporary studies employing strict radiographic response criteria demonstrate low response rates. For example, the combination of temozolomide and thalidomide has been associated with a response rate of only 7% in carcinoid tumors.[75] One potential explanation is increased expression of MGMT, a DNA repair enzyme, in carcinoid tumors compared to PNETs.[76]

High-grade (or poorly differentiated) NETs appear to be highly sensitive to platinum-based cytotoxic chemotherapy regimens. These aggressive malignancies are histologically characterized by a high mitotic rate (typically defined as > 10 to 20 mitoses per 10 high-powered fields), extensive necrosis, and pleomorphism. The clinical characteristics of extrapulmonary poorly differentiated NETs are similar to small cell carcinomas of the lung. In one study investigating cisplatin and etoposide in gastrointestinal NETs, a response rate of 67% was observed in poorly differentiated tumors vs 7% in well-differentiated tumors.[77] Another study of cisplatin and etoposide in poorly differentiated NETs of the gastrointestinal tract demonstrated a response rate of 42%.[78] The durations of response in both studies were short (8 to 9 months), with median survivals of only 15 to 19 months.

Radiolabeled SSAs

Nearly 80% of gastroenteropancreatic NETs express somatostatin receptors as evidenced by radiotracer uptake on ^{111}In-pentetreotide scans (OctreoScans). The high incidence of somatostatin receptor expression has provided the rationale for development of radiolabeled SSAs as a means of delivering targeted radiotherapy to NETs.

Early clinical trials of somatostatin-labeled radionuclides used high cytotoxic doses of ^{111}In-pentetreotide,

the isotope used in OctreoScans.[79,80] While clinical benefit was observed in some cases, objective radiographic responses were rare, possibly due to the short tissue penetration of Auger electrons emitted by the ^{111}In isotope. The next generation of radiolabeled SSAs used yttrium (^{90}Y), a high-energy β-particle emitter with a maximum tissue penetration range of 12 mm. Objective radiographic response rates associated with ^{90}Y-DOTA-Tyr^3-octreotide (also known as ^{90}Y-DOTATOC) were initially reported to be in the 10% to 30% range.[81-83] However, a large multicenter phase II trial of 90 patients with metastatic carcinoid tumors recently reported an objective response rate of only 4% (with a stable disease rate of 70% and high rate of symptom control).[84] Adverse events consisted primarily of nausea and vomiting attributed to amino acid solutions that were administered to prevent radiation nephrotoxicity.

The latest generation of radiolabeled SSAs utilizes ^{177}lutetium-octreotate (^{177}Lu-DOTA-Tyr^3-octreotate), a β and γ particle-emitting compound with enhanced affinity for sst_2. An objective radiographic response rate of 30% and a median time to progression of 40 months were reported in an ongoing single-center study of 310 patients.[85] Adverse effects were mild and consisted primarily of nausea and vomiting occurring within 24 hours of radionuclide administration. Selection criteria for radiolabeled SSA therapy include evidence of strong radiotracer uptake on OctreoScan (at least as high as normal liver tissue).

Liver-Targeted Therapies

The liver is the predominant site of metastases in PNETs and gastrointestinal NETs.[6,20] Patients with liver metastases may experience symptoms such as pain, anorexia, and weight loss related to tumor burden. Additional symptoms include flushing and diarrhea caused by secretion of hormones directly into the systemic circulation. Hepatic-directed therapies include liver resection or ablation, hepatic artery embolization, and liver transplantation. These therapies are generally reserved for patients whose tumors are predominantly confined to the liver.

Liver resection is generally advocated for patients with limited hepatic disease in which more than 90% of tumors can be successfully resected or ablated.[86,87] Various ablation techniques have been described, including cryoablation, alcohol ablation, and radiofrequency ablation (RFA).[89-91] RFA involves conversion of radiofrequency waves to heat using a high alternating current that causes ionic vibration after the change in the current direction.[88] Ablation methods are generally reserved for unresectable metastases smaller than 5 to 7 cm in diameter. Proponents of cytoreductive hepatic resection and ablation cite numerous institutional series reporting palliation of symptoms and prolonged survival durations among patients undergoing surgery with curative or near-curative intent.[92-96] However, there are no randomized studies comparing surgical to nonsurgical approaches, and prolonged survival durations observed in surgically treated patients may be related to inherently favorable prognostic factors such as low tumor burden.

Hepatic artery embolization is typically performed in patients with diffuse, unresectable liver metastases. The rationale for embolization is that liver metastases derive the majority of their blood supply from the hepatic arterial circulation, whereas the normal liver parenchyma derives its blood supply primarily from the portal venous circulation. In patients with bilobar hepatic metastases, staged lobar embolizations are typically performed at 4- to 6-week intervals.

The embolization procedure begins with a celiac angiogram designed to identify the hepatic vasculature, patency of the portal vein, and location of hepatic metastases. Selective catheterization of the right or left hepatic artery is then performed under fluoroscopy. Various par-

Table 4. — Summary of Clinical Trials Evaluating Hepatic Artery Embolization in Metastatic NETs

Author (yr)	No. of Patients	Disease	Technique	Complete/Partial Response
Ruszniewski[97] (1993)	24	Carcinoid and PNET	TACE	33%
Gupta[99] (2003)	81	Carcinoid	TAE or TACE	67%
Strosberg[100] (2006)	84	Carcinoid and PNET	TAE	48%
Eriksson[98] (1998)	41	Carcinoid and PNET	TAE	51%
Therasse[102] (1993)	23	Carcinoid	TACE	35%
Loewe[101] (2003)	23	Carcinoid	TAE	73%
Rhee[104] (2008)	42	Carcinoid and PNET	^{90}Y spheres	51%
Kennedy[103] (2008)	148	Carcinoid and PNET	^{90}Y spheres	63%

PNET = pancreatic neuroendocrine tumors, TACE = transarterial chemoembolization, TAE = transarterial embolization.

ticulate and occlusive materials have been used including Gelfoam (Pharmacia and Upjohn Co, Kalamazoo, MI), polyvinyl alcohol (PVA) particles, and trisacryl gelatin microspheres (Embospheres; BioSphere Medical Inc, Rockland, MA). Embolization can be performed either with the addition of intra-arterial cytotoxic agents (chemoembolization) or without (bland embolization). For chemoembolization, an emulsion of cytotoxic drugs such as doxorubicin or cisplatin is combined with iodized oil and injected into the selected artery until near-complete stasis of flow. There are no randomized studies comparing bland embolization to chemoembolization techniques and no consensus favoring a particular approach. Reported response rates, derived primarily from institutional series, are relatively equivalent (Table 4).[97-104] Side effects of hepatic artery embolization include nausea, abdominal pain, fevers, and fatigue, all caused by induction of ischemic hepatitis. Serum transaminases typically increase significantly, peaking 2 to 3 days after each embolization. Most side effects resolve within 1 week of treatment.[100] Contraindications to the transarterial embolization include liver dysfunction, moderate to severe ascites, and portal venous thrombosis.

A novel approach to hepatic metastases involves arterial embolization of ^{90}Y embedded in either a resin microsphere (SIR-Spheres, Sirtex Medical Ltd, Lane Cove, Australia) or a glass microsphere (TheraSphere, MDS-Nordion Inc, Ontario, Canada). This technique enables direct delivery of a radionuclide with a long-range tissue penetration of up to 11 mm to hepatic metastases. A preprocedural celiac angiogram is necessary to map the vascular supply to the liver and identify aberrant vessels to the gastrointestinal tract that need to be avoided or embolized before treatment. ^{99m}Technetium macro-albumin is then infused intra-arterially with single photon emission computed tomography (SPECT) imaging to evaluate for possible intrahepatic arterial shunting to the lungs or gastrointestinal tract. These procedures are performed to avoid unintentional infusion of radioactive microspheres outside of the liver, which could lead to radiation pneumonitis or enteritis. The actual radioembolization procedure is performed similarly to bland embolization or chemoembolization. However, the microspheres are not infused until stasis of blood flow due to the fact that cell death through radiation requires normal oxygen tension. Consequently, patients with mild to moderate liver dysfunction or portal vein thrombosis who are ineligible for bland embolization or chemoembolization may be able to tolerate radioembolization.

Toxicities associated with ^{90}Y microsphere radioembolization appear to be lower than with other embolization techniques, primarily due to the fact that the procedure does not induce ischemic hepatitis. Thus, the procedure can be performed on an outpatient basis. A serious potential complication is radiation enteritis, which can occur if particles are accidentally infused into arteries supplying the gastrointestinal tract. This toxicity appears to occur rarely in high-volume centers. Response rates associated with radioembolization in metastatic NETs have been encouraging. In one retrospective multicenter study of 148 patients treated with SIR-Spheres, the objective radiographic response rate was 63%, with a median survival of 70 months.[103] Another study of 42 patients treated with either TheraSphere microspheres or SIR-Spheres reported a response rate of 51%. However, only 29 of the 42 enrolled patients were evaluable for response.[104]

Liver transplantation has been described in metastatic NET patients, but the benefits of transplantation are uncertain. Most centers report a high postoperative mortality rate of 10% to 20%. In the largest reported meta-analysis of 103 patients, the 5-year survival rate was 47%, with only 24% of patients free of disease recurrence.[105] Another multicenter analysis of 85 cases reported a 5-year survival rate of 47% and recurrence-free survival rate of 20% at 5 years.[106] Since recurrence-free survival curves have not achieved a plateau, it is unclear whether transplantation can be considered as potentially curative. Negative prognostic factors for recurrence have included hepatomegaly, pancreatic primary site (as opposed to small intestinal), and elevated Ki-67 index.

Conclusions

Therapeutic options for treatment of metastatic gastroenteropancreatic NETs are expanding. SSAs such as octreotide represent the appropriate first-line treatment for most patients with well-differentiated tumors. In the past, SSAs were employed primarily for palliation of secretory hormonal syndromes. More recent data support their role as antiproliferative agents, capable of stabilizing tumor growth in a large percentage of patients and significantly improving PFS regardless of hormonal output. At this time, high-level evidence favors the use of octreotide as an antiproliferative agent in metastatic well-differentiated midgut NETs. The role of SSAs in the treatment of other types of neuroendocrine malignancies is still uncertain.

IFN-α is another agent that can palliate hormonal symptoms and inhibit tumor growth, albeit with higher rates of toxicity than SSAs. Novel targeted agents include sunitinib, bevacizumab, and everolimus. Among these, sunitinib has been proven to improve PFS in a phase III study of PNETs. Phase III data on everolimus and bevacizumab are anticipated in the near future.

Cytotoxic chemotherapy has long been known to be active in poorly differentiated NETs. Accumulating data point to the fact that PNETs are substantially more sensitive than carcinoid tumors to chemotherapy. While STZ-based regimens are associated with high response rates, temozolomide-based regimens appear to be at least equally active and with lower rates of toxicity. Due to the increasing interest in targeted agents, cytotoxic

drugs have not been evaluated in contemporary phase III studies. However, the high response rates reported with temozolomide warrant further studies in larger multicenter studies.

Liver-directed therapies such as surgical cytoreduction, ablation, and embolization are frequently employed for treatment of patients with liver-predominant metastases. New radioembolization techniques utilizing ^{90}Y microspheres are encouraging due to their reduced toxicity.

In this era of expanding treatment options, understanding how to best sequence treatments becomes increasingly vital. One complicating factor is that many patients with asymptomatic indolent tumors require no treatment at all and can be managed with close observation. Future randomized trials comparing various therapies and evaluating combination vs sequential approaches may help in the development of treatment algorithms.

References

1. Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet*. 1963;1:238-239.
2. Strosberg JR, Nasir A, Hodul P, et al. Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res*. 2008; 2(3):113-125.
3. Kvols LK. The carcinoid syndrome: a treatable malignant disease. *Oncology (Huntingt)*. 1988;2(2):33-41.
4. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993;87 (4):1188-1196.
5. Oberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol*. 2005;19(5):753-781.
6. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. *Pancreas*. 2009;38(3):255-258.
7. Halfdanarson TR, Rubin J, Farnell MB, et al. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer*. 2008;15(2):409-427.
8. Strosberg J, Kvols L. Antiproliferative effect of somatostatin analogs in gastroenteropancreatic neuroendocrine tumors. *World J Gastroenterol*. 28;16 (24):2963-2970.
9. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors. *N Engl J Med*. 2011;364:501-513.
10. Yao JC, Phan AT, Chang DZ, et al. Phase II study of RAD001 (everolimus) and depot octreotide (Sandostatin LAR) in patients with advanced low grade neuroendocrine carcinoma (LGNET). *J Clin Oncol. 2006 ASCO Ann Meet Proc Part I*. 2006;24(18S June 20 suppl):4042. Abstract.
11. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol*. 2010;28(1):69-76.
12. Yao JC, Shah MH, Ito T, et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. *N Engl J Med*. 2011;364:514-523.
13. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008;26(8):1316-1323.
14. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22(23):4762-4771.
15. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326(8):519-523.
16. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer*. 2011;117 (2): 268-275.
17. Kloppel G, Heitz PU, Capella C, et al. Pathology and nomenclature of human gastrointestinal neuroendocrine (carcinoid) tumors and related lesions. *World J Surg*. 1996;20(2):132-141.
18. Capella C, Heitz PU, Hofler H, et al. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch*. 1995;425(6): 547-560.
19. Strosberg J, Nasir A, Coppola D, et al. Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. *Hum Pathol*. 2009;40(9):1262-1268.
20. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology*. 2009;89(4):471-476.
21. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063-3072.
22. Evers BM, Parekh D, Townsend CM Jr, et al. Somatostatin and analogues in the treatment of cancer. A review. *Ann Surg*. 1991;213(3):190-198.
23. Reichlin S. Somatostatin. *N Engl J Med*. 1983;309(24):1495-1501.
24. Brazeau P, Guillemin R. Editorial: Somatostatin: newcomer from the hypothalamus. *N Engl J Med*. 1974;290(17):963-964.
25. Lamberts SW, van der Lely AJ, de Herder WW, et al. Octreotide. *N Engl J Med*. 1996;334(4):246-254.
26. Maurer R, Reubi JC. Somatostatin receptors. *JAMA*. 1985;253(18):2741.
27. Bousquet C, Puente E, Buscail L, et al. Antiproliferative effect of somatostatin and analogs. *Chemotherapy*. 2001;47(suppl 2):30-39.
28. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome: evaluation of a long-acting somatostatin analogue. *N Engl J Med*. 1986;315(11):663-666.
29. di Bartolomeo M, Bajetta E, Buzzoni R, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors: a study by the Italian Trials in Medical Oncology Group. *Cancer*. 1996;77(2):402-408.
30. Maton PN, Gardner JD, Jensen RT. Use of long-acting somatostatin analog SMS 201-995 in patients with pancreatic islet cell tumors. *Dig Dis Sci*. 1989;34(3 suppl):28S-39S.
31. Rubin J, Ajani J, Schirmer W, et al. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol*. 1999;17(2):600-606.
32. O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer*. 2000;88(4): 770-776.
33. Kulke MH, Mayer RJ. Carcinoid tumors. *N Engl J Med*. 1999;340(11): 858-868.
34. Oberg K, Kvols L, Caplin M, et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol*. 2004;15(6):966-973.
35. Woltering EA, Mamikunian PM, Zietz S, et al. Effect of octreotide LAR dose and weight on octreotide blood levels in patients with neuroendocrine tumors. *Pancreas*. 2005;31(4):392-400.
36. Ruszniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut*. 1996;39(2):279-283.
37. Kvols LK, Wiedenmann K, Oberg J. Safety and efficacy of pasireotide (SOM230) in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR: results of a phase II study. *J Clin Oncol. 2006 ASCO Ann Meet Proc Part I*. 2006;24(18S June 20 suppl):4082. Abstract.
38. Sharma K, Srikant CB. G protein coupled receptor signaled apoptosis is associated with activation of a cation insensitive acidic endonuclease and intracellular acidification. *Biochem Biophys Res Commun*. 1998;242(1):134-140.
39. Weckbecker G, Lewis I, Albert R, et al. Opportunities in somatostatin research: biological, chemical and therapeutic aspects. *Nat Rev Drug Discov*. 2003;2(12):999-1017.
40. Lattuada D, Casnici C, Venuto A, et al. The apoptotic effect of somatostatin analogue SMS 201-995 on human lymphocytes. *J Neuroimmunol*. 2002;133(1-2):211-216.
41. Florio T. Somatostatin/somatostatin receptor signalling: phosphotyrosine phosphatases. *Mol Cell Endocrinol*. 2008;286(1-2):40-48.
42. Schettini G, Florio T, Meucci O, et al. Somatostatin inhibition of anterior pituitary adenylate cyclase activity: different sensitivity between male and female rats. *Brain Res*. 1988;439(1-2):322-329.
43. Serri O, Brazeau P, Kachra Z, et al. Octreotide inhibits insulin-like growth factor-I hepatic gene expression in the hypophysectomized rat: evidence for a direct and indirect mechanism of action. *Endocrinology*. 1992; 130(4):1816-1821.
44. Woltering EA, Watson JC, Alperin-Lea RC, et al. Somatostatin analogs: angiogenesis inhibitors with novel mechanisms of action. *Invest New Drugs*. 1997;15(1):77-86.
45. Kumar M, Liu ZR, Thapa L, et al. Antiangiogenic effect of somatostatin receptor subtype 2 on pancreatic cancer cell line: inhibition of vascular endothelial growth factor and matrix metalloproteinase-2 expression in vitro. *World J Gastroenterol*. 2004;10(3):393-399.
46. Saltz L, Trochanowski B, Buckley M, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer*. 1993;72(1):244-248.
47. Eriksson B, Renstrup J, Imam H, et al. High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Ann Oncol*. 1997;8(10):1041-1044.
48. Tomassetti P, Migliori M, Corinaldesi R, et al. Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. *Aliment Pharmacol Ther*. 2000;14(5):557-560.

49. Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol*. 1999;17(4):1111.

50. Faiss S, Pape UF, Böhmig M, et al. 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*. 2003;21(14):2689-2696.

51. Aparicio T, Ducreux M, Baudin E, et al. Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer*. 2001;37(8):1014-1019.

52. Arnold R, Trautmann ME, Creutzfeldt W, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut*. 1996 Mar;38(3):430-438.

53. Ducreux M, Ruszniewski P, Chayvialle JA, et al. The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. *Am J Gastroenterol*. 2000;95(11):3276-3281.

54. Ricci S, Antonuzzo A, Galli L, et al. Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide. *Ann Oncol*. 2000;11(9):1127-1130.

55. Tomassetti P, Migliori M, Gullo L. Slow-release lanreotide treatment in endocrine gastrointestinal tumors. *Am J Gastroenterol*. 1998;93(9):1468-1471.

56. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.

57. Detjen KM, Welzel M, Farwig K, et al. Molecular mechanism of interferon alfa-mediated growth inhibition in human neuroendocrine tumor cells. *Gastroenterology*. 2000;118(4):735-748.

58. Hofland LJ, de Herder WW, Waaijers M, et al. Interferon-alpha-2a is a potent inhibitor of hormone secretion by cultured human pituitary adenomas. *J Clin Endocrinol Metab*. 1999;84(9):3336-3343.

59. Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. *N Engl J Med*. 1983;309(3):129-133.

60. Biesma B, Willemse PH, Mulder NH, et al. Recombinant interferon alpha-2b in patients with metastatic apudomas: effect on tumours and tumour markers. *Br J Cancer*. 1992;66(5):850-855.

61. Eriksson B, Oberg K, Alm G, et al. Treatment of malignant endocrine pancreatic tumours with human leucocyte interferon. *Lancet*. 1986;2(8519):1307-1309.

62. Janson ET, Oberg K. Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. *Acta Oncol*. 1993;32(2):225-229.

63. Frank M, Klose KJ, Wied M, et al. Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. *Am J Gastroenterol*. 1999;94(5):1381-1387.

64. Kölby L, Persson G, Franzén S, et al. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg*. 2003;90(6):687-693.

65. Faiss S, Scherübl H, Riecken EO, et al. Interferon-alpha versus somatostatin or the combination of both in metastatic neuroendocrine gut and pancreatic tumours. *Digestion*. 1996;57(suppl 1):84-85.

66. Arnold R, Rinke A, Klose KJ, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol*. 2005;3(8):761-771.

67. Vignot S, Faivre S, Aguirre D, et al. mTOR-targeted therapy of cancer with rapamycin derivatives. *Ann Oncol*. 2005;16(4):525-537.

68. Verhoef S, van Diemen-Steenvoorde R, Akkersdijk WL, et al. Malignant pancreatic tumour within the spectrum of tuberous sclerosis complex in childhood. *Eur J Pediatr*. 1999;158(4):284-287.

69. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer*. 2006;95(9):1148-1154.

70. Pavel M, Hainsworth JD, Baudin E, et al. A randomized, double-blind, placebo-controlled, multicenter phase iii trial of everolimus 1 octreotide LAR vs placebo 1 octreotide LAR in patients with advanced neuroendocrine tumors (NET) (RADIANT-2). Paper presented at: 35th European Society for Medical Oncology Congress; October 8-12, 2010; Milan, Italy. *Ann Oncol*. 2010;21(suppl 8):viii4. Abstract LBA8.

71. Terris B, Scoazec JY, Rubbia L, et al. Expression of vascular endothelial growth factor in digestive neuroendocrine tumours. *Histopathology*. 1998; 32(2):133-138.

72. Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol*. 2008;26(20):3403-3410.

73. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1980;303(21):1189-1194.

74. Ramanathan RK, Cnaan A, Hahn RG, et al. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. *Ann Oncol*. 2001;12(8):1139-1143.

75. Kulke MH, Stuart K. Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol*. 2006;24(3):401-406.

76. Kulke MH, Hornick JL, Frauenhoffer C, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res*. 2009;15(1):338-345.

77. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*. 1991;68(2):227-232.

78. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*. 1999;81(8):1351-1355.

79. Krenning EP, Bakker WH, Kooij PP, et al. Somatostatin receptor scintigraphy with indium-111-DTPA-D-Phe-1-octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-octreotide. *J Nucl Med*. 1992;33(5):652-658.

80. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med*. 1993;20(8):716-731.

81. Kwekkeboom DJ, Mueller-Brand J, Paganelli G, et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. *J Nucl Med*. 2005;46(suppl 1):62S-66S.

82. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med*. 2006;36(2):147-156.

83. Waldherr C, Pless M, Maecke HR, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. *J Nucl Med*. 2002;43(5):610-616.

84. Bushnell DL Jr, O'Dorisio TM, O'Dorisio MS, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol*. 2010;28(10):1652-1659.

85. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26(13):2124-2130.

86. Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg*. 2003;197(1):29-37.

87. Norton JA, Warren RS, Kelly MG, et al. Aggressive surgery for metastatic liver neuroendocrine tumors. *Surgery*. 2003;134(6):1057-1063; discussion 1063-1065.

88. Kvols LK, Turaga KK, Strosberg J, et al. Role of interventional radiology in the treatment of patients with neuroendocrine metastases in the liver. *J Natl Compr Canc Netw*. 2009;7(7):765-772.

89. Ruszniewski P, O'Toole D. Ablative therapies for liver metastases of gastroenteropancreatic endocrine tumors. *Neuroendocrinology*. 2004;80 (suppl 1):74-78.

90. Henn AR, Levine EA, McNulty W, et al. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *AJR Am J Roentgenol*. 2003;181(4):1005-1010.

91. Hellman P, Ladjevardi S, Skogseid B, et al. Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. *World J Surg*. 2002;26(8):1052-1056.

92. Que FG, Nagorney DM, Batts KP, et al. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg*. 1995;169(1):36-42; discussion 42-33.

93. McEntee GP, Nagorney DM, Kvols LK, et al. Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery*. 1990;108(6):1091-1096.

94. Chen H, Hardacre JM, Uzar A, et al. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? *J Am Coll Surg*. 1998;187(1):88-92; discussion 92-83.

95. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. *Surg Oncol Clin N Am*. 2003;12(1):231-242.

96. Osborne DA, Zervos EE, Strosberg J, et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. *Ann Surg Oncol*. 2006;13(4):572-581.

97. Ruszniewski P, Rougier P, Roche A, et al. Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective phase II study in 24 patients. *Cancer*. 1993;71(8):2624-2630.

98. Eriksson BK, Larsson EG, Skogseid BM, et al. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer*. 1998;83(11):2293-2301.

99. Gupta S, Yao JC, Ahrar K, et al. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. *Cancer J*. 2003;9(4):261-267.

100. Strosberg JR, Choi J, Cantor AB, et al. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. *Cancer Control*. 2006;13(1):72-78.

101. Loewe C, Schindl M, Cejna M, et al. Permanent transarterial embolization of neuroendocrine metastases of the liver using cyanoacrylate and

lipiodol: assessment of mid- and long-term results. *AJR Am J Roentgenol*. 2003;180(5):1379-1384.
102. Therasse E, Breittmayer F, Roche A, et al. Transcatheter chemoembolization of progressive carcinoid liver metastasis. *Radiology*. 1993;189(2):541-547.
103. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol*. 2008;31(3):271-279.
104. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. *Ann Surg*. 2008;247(6):1029-1035.
105. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma: an analysis of 103 patients. *Transplantation*. 1998;66(10):1307-1312.
106. Le Treut YP, Grégoire E, Belghiti J, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. *Am J Transplant*. 2008;8(6):1205-1213.