Gastrointestinal neuroendocrine tumors: a role for targeted therapies?

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Abstract

Traditional therapies have offered patients with advanced gastrointestinal neuroendocrine tumors limited benefit. Selected patients with hepatic metastases may benefit from surgical debulking, embolization, or other ablative therapies. While somatostatin analogs are highly effective in controlling symptoms of hormonal secretion, they are only rarely associated with tumor regression. The clinical benefit associated with the administration of systemic agents such as interferon-α or cytotoxic chemotherapy is less clear, and the widespread use of such regimens has been limited by their relatively modest anti-tumor activity, as well as concerns regarding their potential toxicity. The mixed clinical results seen with these agents in neuroendocrine tumors have led to great interest in the development of novel treatment approaches for patients with advanced disease. Recent clinical studies of novel agents, particularly those targeting the vascular endothelial growth factor pathway and mammalian target of rapamycin, have demonstrated promising activity in patients with advanced neuroendocrine tumors. Ongoing randomized studies should help better define the role these and other targeted agents will play in the future treatment of patients with this disease.

Introduction

Neuroendocrine tumors comprise a diverse group of malignancies and, when defined broadly, include not only gastrointestinal neuroendocrine tumors but also pheochromocytoma, thyroid cancer, and even small cell lung cancer. Gastrointestinal neuroendocrine tumors are usually subclassified as either pancreatic neuroendocrine tumors or carcinoid tumors. The treatment approaches for both tumor types share many similarities due to their often indolent behavior, characteristic well-differentiated histologic features, and shared ability to secrete neuropeptides resulting in characteristic clinical syndromes.

In contrast to most other malignancies, there is no formal staging system for gastrointestinal neuroendocrine tumors. The absence of such a staging system in part reflects the straightforward treatment approach to localized neuroendocrine tumors, which is almost always surgical resection (Fig. 1). Adjunctive therapy has no established role in this disease, even in cases where local lymph nodes are involved and the risk of recurrence is felt to be high. Unfortunately, curative surgery is seldom an option for patients with metastatic disease, and standard cytotoxic therapy offers limited benefit. A number of other treatment approaches, including the use of somatostatin analogs, surgical debulking, and ablation of hepatic metastases offer palliative benefit for such patients. Novel treatment approaches, including the use of agents targeting vascular endothelial growth factor (VEGF) and other pathways involved in neuroendocrine tumorigenesis, may provide additional therapeutic options.

Clinical presentation and diagnosis of metastatic disease

Whereas some patients with advanced neuroendocrine tumors may remain symptom-free for years, others develop symptoms from either tumor bulk or hormonal hypersecretion. In patients with metastatic carcinoid tumors, the secretion of serotonin and other vasoactive substances may cause carcinoid syndrome, which is manifested by episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease (Thorson et al. 1954). The best-characterized
syndromes associated with pancreatic neuroendocrine tumors are those associated with insulinoma, glucagonoma, vasoactive intestinal peptideoma, and gastrinoma. The so-called ‘non-functioning’ pancreatic neuroendocrine tumors often present at a late stage, and may be associated with high serum levels of pancreatic polypeptide.

The predominant site of metastatic spread in patients with neuroendocrine tumors involving the gastrointestinal tract is the liver. Patients with suspected metastatic disease are generally evaluated with an abdominal computerized tomography (CT) scan to rule out liver metastases. Liver function tests are unreliable indicators of tumor involvement, and serum alkaline phosphatase levels are frequently normal despite extensive liver involvement by carcinoid tumor. Carcinoid liver metastases are often hypervascular and may become isodense relative to the liver with the administration of intravenous contrast materials. CT scans should thus be performed both before and after the administration of intravenous contrast agents (Sugimoto et al. 1995, Woodard et al. 1995).

Somatostatin receptor scintigraphy provides another useful imaging modality for the detection of metastatic disease in patients with neuroendocrine tumors. With the exception of insulinomas (of which only 50% express type-2 somatostatin receptors), over 90% of neuroendocrine tumors, including non-functioning pancreatic tumors and carcinoid tumors, contain high concentrations of somatostatin receptors, and can be imaged with a radiolabeled form of the somatostatin analog octreotide (111-indium pentetreotide; Lamberts et al. 1990, Kvols et al. 1993, Kaltsas et al. 2001). The uptake of radiolabeled octreotide is also predictive of a clinical response to therapy with somatostatin analogs (Lamberts et al. 1990).

Serial measurement of the serotonin metabolite 5-hydroxyindoleacetic acid (HIAA) in 24-h urine collections has been commonly used in the diagnosis and subsequent monitoring of patients with metastatic carcinoid tumors. Although elevated urinary 5-HIAA levels are highly specific for carcinoid tumors, they are not particularly sensitive; in one study, only 73% of patients with metastatic carcinoid tumors had elevated levels (Feldman & O’Dirisio 1986). Furthermore, 5-HIAA levels are generally elevated in patients with metastatic midgut carcinoid tumors, but are less useful in patients with either foregut (bronchial, gastric) or hindgut (rectal) carcinoid tumors, which less commonly secrete serotonin.

Chromogranin A (CGA) is a 49 kDa protein that is contained in the neurosecretory vesicles of neuroendocrine tumor cells, and has been identified in the plasma of patients with endocrine neoplasms. Plasma CGA
concentrations are a more sensitive marker than urinary 5-HIAA levels in patients with carcinoid tumors, and can also be used as a marker in patients with both functional and non-functional pancreatic endocrine tumors (Seregni et al. 2001, Stivanello et al. 2001, Tomassetti et al. 2001, Oberg et al. 2004). CGA concentrations should be used with caution as a marker of disease activity in patients treated with somatostatin analogs, since these agents significantly reduce plasma CGA levels (Oberg et al. 2004). In such cases, changes in CGA concentrations may be more reflective of alterations in hormonal synthesis and release from tumor cells than an actual reduction in tumor mass. In patients on stable doses of somatostatin analogs, consistent increases in plasma CGA levels over time may reflect loss of secretory control and/or tumor growth. Plasma CGA levels have also been shown to have prognostic value; in one series of 71 patients with metastatic carcinoid tumors, CGA levels of more than 5000 μg/ml were independently associated with poor prognosis. (Janson et al. 1997)

Surgical options

In selected cases, metastatic liver disease can be surgically resected. In one large surgical series involving 170 patients undergoing hepatic resection, more than 90% achieved improvement in symptoms. While the recurrence rate following surgery was high (84%), the 5- and 10-year survival rates were encouraging (61 and 35% respectively; Sarmiento et al. 2003). Several retrospective surgical series have suggested that patients who undergo either complete resection or aggressive ‘debulking’ of hepatic metastases have improved quality of life and improved survival times when compared with patients who do not undergo surgery. (Knox et al. 2004, Touzios et al. 2005, Musunuru et al. 2006, Osborne et al. 2006) In one such series, patients undergoing cytoreductive surgery had a mean survival duration of 43 months, as compared with 24 months for patients undergoing embolization (Osborne et al. 2006). Similarly, in one study, resection of the primary tumor in patients with documented liver metastases was associated with improved survival (Givi et al. 2006). While many of these series match patients retrospectively according to tumor bulk and other clinical parameters, the lack of formal randomization and potential for selection bias makes definitive interpretation of these results difficult.

The number of patients with liver-isolated metastatic disease in whom orthotopic liver transplantation (OLT) has been attempted is small, and the role of OLT in such patients remains unclear (Alsina et al. 1990, Lang et al. 1997, Le Treut et al. 1997, van Vilsteren et al. 2006). Results from one multicenter study demonstrated a 5-year overall survival rate of 69% for patients with carcinoid tumors (Le Treut et al. 1997). Despite high survival rates in selected patients, however, the majority of patients undergoing transplant ultimately appear to develop recurrent disease (Le Treut et al. 1997, Florman et al. 2004). The limited availability of orthotopic transplants in many regions has also limited the widespread use of this procedure.

Non-surgical, hepatic-directed therapy

Hepatic artery embolization

Hepatic arterial embolization is commonly used as a palliative technique in patients with hepatic metastases, who are not candidates for surgical resection. Hepatic artery embolization is based on the principle that tumors in the liver derive most of their blood supply from the hepatic artery, whereas healthy hepatocytes derive most of their blood supply from the portal vein. The response rates associated with embolization, as measured either by a decrease in hormonal secretion or by radiographic regression, are generally >50% (Ajani et al. 1988, Ruszniewski et al. 1993, Moertel et al. 1994, Diamandidou et al. 1998, Drougas et al. 1998, Eriksson et al. 1998, Brown et al. 1999, Dominguez et al. 2000, Gupta et al. 2003, Loewe et al. 2003). However, the duration of response can be brief, ranging from 4 to 51 months in uncontrolled patient series (Moertel et al. 1994, Gupta et al. 2003). In one of the largest series of 81 patients undergoing embolization or chemoembolization for carcinoid tumors, the median duration of response was 17 months, and the probability of progression-free survival at 1, 2, and 3 years was 75, 35, and 11% respectively (Gupta et al. 2003). Early studies reported a significant incidence of post-embolization complications that included renal failure, hepatic necrosis, and sepsis. Improved techniques have, in recent years, reduced the incidence of such complications, making embolization an important and generally safe treatment option for patients with neuroendocrine tumors (Gupta et al. 2003).

Radiofrequency ablation (RFA) and cryoablation

Other approaches to the treatment of hepatic metastases include the use of RFA and cryoablation, either alone or in conjunction with surgical debulking. While these approaches appear to be less morbid than either hepatic resection or hepatic artery embolization, their efficacy, particularly in patients with large volume...
hepatic disease, has not been well studied. Most published reports are small case studies of fewer than 40 patients (Chung et al. 2001, Berber et al. 2002, Gulec et al. 2002, Hellman et al. 2002).

Systemic treatment

Somatostatin analogs and interferon (IFN)-α

Carcinoid syndrome, as well as other hormonal syndromes associated with pancreatic neuroendocrine tumors, can often be well controlled with somatostatin analogs. In an initial study, the subcutaneous administration of the somatostatin analog octreotide, administered at a dosage of 150 μcg three times a day, improved the symptoms of carcinoid syndrome in 88% of patients (Kvols et al. 1986). More recently, the use of a long-acting depot form of octreotide, which can be administered on a monthly basis, has largely obviated the need for patients to inject themselves on a daily basis. Long-acting octreotide is typically initiated at a dose of 20 mg IM after a brief trial of the short-acting formulation, with gradual escalation of the dose as needed for optimal control of symptoms (Rubin et al. 1999, Oberg et al. 2004). Patients may also use additional short-acting octreotide for breakthrough symptoms. Lanreotide, another somatostatin analog, appears to be similar to octreotide in its clinical efficacy (Faiss et al. 1999, Wymenga et al. 1999, Ducreux et al. 2000, O'Toole et al. 2000, Faiss et al. 2003). Somatostatin analogs are well tolerated by patients and studies report only mild and occasional toxicities, including hyperglycemia, steatorrhea, an increased risk of cholelithiasis, and irritation at the injection site.

The ability of leukocyte IFN to stimulate T-lymphocyte function and control the secretion of tumor products led to its initial use in patients with carcinoid syndrome (Oberg et al. 1983). The addition of IFN-α to therapy with somatostatin analogs has subsequently been reported to be effective in controlling symptoms in patients with carcinoid syndrome, who may be resistant to somatostatin analogs alone (Janson & Oberg 1993, Frank et al. 1999). Therapy with low-dose IFN-α has been reported to result in biochemical responses in ~40% of patients with metastatic neuroendocrine tumors (Oberg & Eriksson 1991). The more widespread acceptance of IFN-α in the treatment of metastatic neuroendocrine tumors has been limited by studies challenging its efficacy, as well as the potential for side effects, which may include myelosuppression, fatigue, depression, and alteration of thyroid function (Valimaki et al. 1991).

Whether somatostatin analogs have a direct cytostatic effect, either alone or when combined with IFN-α, is controversial (Saltz et al. 1993). Radiologic evidence of tumor regression following treatment with these agents is rare. In a small study involving 21 patients with metastatic gastroenteropancreatic neuroendocrine tumors, a combined regimen of a somatostatin analog and IFN-α appeared to significantly slow the rate of tumor progression in 67% of patients during follow-up (Frank et al. 1999). In a prospective study of 68 patients randomized to receive either octreotide alone or a combination of octreotide and IFN-α, there was no significant difference in the overall survival; however, patients treated with the combination regimen had a reduced risk of tumor progression, suggesting that IFN-α had a cytostatic effect (Kolby et al. 2003). The efficacy of lanreotide, IFN-α, or combined therapy was evaluated in a prospective randomized trial involving 80 therapy-naive patients with documented progressive metastatic neuroendocrine tumors (Faiss et al. 2003). The rates of objective partial response (4, 4, and 7% for lanreotide, IFN-α, and combined therapy respectively) were low in all three groups; however, all treatments resulted in apparent disease stabilization in a higher proportion of patients (28, 26, and 18% for lanreotide, IFN-α, and combined therapy respectively).

Cytotoxic chemotherapy

The efficacy of cytotoxic chemotherapy in patients with carcinoid tumors has been relatively limited (Table 1). In an initial trial, the Eastern Cooperative Oncology Group (ECOG) randomized 118 patients to receive streptozocin combined with either fluorouracil or cyclophosphamide (Moertel & Hanley 1979). Response rates, as measured either by tumor regression or a decrease in urinary 5-HIAA levels, were 33% in the streptozocin and fluorouracil arm and 26% in the streptozocin and cyclophosphamide arm. There were no significant differences in survival between the two groups. In a subsequent trial, the dosing interval between cycles of streptozocin and fluorouracil was increased, and this treatment was compared with that of doxorubicin alone (Engstrom et al. 1984). With this revised schedule, the response rate for streptozocin and fluorouracil was 22%, as compared with 21% for doxorubicin alone; again there were no significant differences in survival. Most recently, streptozocin and fluorouracil was compared with doxorubicin and fluorouracil in a randomized trial of 249 patients (Sun et al. 2005). The response rates associated with the two regimens were similar (16% vs 15.9%). Although there was a slight survival benefit associated
with streptozocin and fluorouracil (24.3 vs 15.7 months) in this trial, over one-third of patients treated with streptozocin developed renal toxicity. This and other toxicities, combined with only modest efficacy, has precluded the common use of streptozocin-based regimens as a first-line treatment for advanced carcinoid disease.

Several studies suggest that pancreatic endocrine tumors are more responsive to chemotherapy than are carcinoid tumors (Table 2). In an initial randomized trial, Moertel et al. (1992) reported that the combination of streptozocin and doxorubicin was associated with a combined biochemical and radiologic response rate of 69% and a median overall survival time of 2.2 years. Two subsequent retrospective analyses of patients receiving this regimen questioned the high response rate of this initial trial, and reported objective radiologic response rates, using modern response criteria, of 10% (Cheng & Saltz 1999, McCollum et al. 2004). A larger retrospective analysis of 84 patients with either locally advanced or metastatic pancreatic endocrine tumors receiving a three-drug regimen of streptozocin, fluorouracil, and doxorubicin showed that this regimen was associated with an overall response rate of 39% and a median survival duration of 37 months, suggesting that this combination is indeed active, though perhaps less active than Moertel’s data suggested initially (Kouvaraki et al. 2004). This study reported grade 3 or 4 toxicities in 23% of the patient cohort, with myelosuppression, mucositis, diarrhea, and fatigue the most frequently reported adverse reactions.

Dacarbazine (DTIC) has been evaluated as a potential alternative to streptozocin-based therapy in both carcinoid and pancreatic endocrine tumors. The ECOG performed a phase II study of DTIC in 50 patients with advanced pancreatic islet cell carcinoma and reported an objective response rate of 34% (Table 2; Ramanathan et al. 2001). A Southwest Oncology Group (SWOG) study reported that treatment with DTIC was associated with an objective radiologic response rate of 16% in 56 patients with metastatic carcinoid tumors (Table 1; Bukowski et al. 1987). Toxicity was a concern in both studies: 88% of patients in the SWOG study reported nausea and/or vomiting and there were two lethal toxicities in the ECOG study. In another study involving 61 patients with carcinoid tumors receiving DTIC as a second-line therapy following treatment with combination chemotherapy, the overall response rate was 8% (Sun et al. 2005).

### Table 1 Selected chemotherapy trials in metastatic carcinoid tumors

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Radiologic tumor response rate (%)</th>
<th>Median overall survival (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II trials</td>
<td></td>
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<tr>
<td>DTIC</td>
<td>56</td>
<td>16</td>
<td>Bukowski et al. (1994)</td>
<td></td>
</tr>
<tr>
<td>DTIC</td>
<td>61</td>
<td>8</td>
<td>Sun et al. (2005)</td>
<td></td>
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<tr>
<td>Temozolomide + thalidomide</td>
<td>14</td>
<td>7</td>
<td>Kulke et al. (2006)</td>
<td></td>
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<tr>
<td>Etoposide</td>
<td>17</td>
<td>12</td>
<td>Kelsen et al. (1987)</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8</td>
<td>Ansell et al. (2001)</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>21</td>
<td>0</td>
<td>Kulke et al. (2004a)</td>
<td></td>
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<tr>
<td>Gemcitabine</td>
<td>18&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>Kulke et al. (2004b)</td>
<td></td>
</tr>
<tr>
<td>Streptozocin + fluorouracil + doxorubicin + cyclophosphamide</td>
<td>56</td>
<td>30</td>
<td>Bukowski et al. (1987)</td>
<td></td>
</tr>
<tr>
<td>Streptozocin + fluorouracil + cyclophosphamide</td>
<td>9</td>
<td>22</td>
<td>Bukowski et al. (1987)</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptozocin + cyclophosphamide</td>
<td>47</td>
<td>26</td>
<td>12.5</td>
<td>Moertel &amp; Hanley (1979)</td>
</tr>
<tr>
<td>Streptozocin + fluorouracil</td>
<td>42</td>
<td>33</td>
<td>11.2</td>
<td>Engstrom et al. (1984)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>81</td>
<td>21</td>
<td>11.1</td>
<td>Sun et al. (2005)</td>
</tr>
<tr>
<td>Streptozocin + fluorouracil</td>
<td>80</td>
<td>22</td>
<td>14.9</td>
<td></td>
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<tr>
<td>Doxorubicin + fluorouracil</td>
<td>88</td>
<td>16</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Streptozocin + fluorouracil</td>
<td>88</td>
<td>16</td>
<td>24.3</td>
<td></td>
</tr>
</tbody>
</table>

DTIC, dacarbazine.<br>aNumber of patients evaluable for efficacy endpoints.<br>bPatients also received granulocyte colony-stimulating factor.<br>cIncludes patients with carcinoid, pancreatic and anaplastic neuroendocrine tumors.<br>dIncludes patients with carcinoid, pancreatic and pheochromoctyoma neuroendocrine tumors.
Temozolomide is a cytotoxic alkylating agent that was specifically developed as an oral and less toxic alternative to DTIC (Stevens et al. 1987). In a phase II study, 29 patients with metastatic carcinoid, pancreatic or pheochromocytoma neuroendocrine tumors were treated with temozolomide, administered at a dose of 150 mg/m² for 7 days, followed by a 7-day rest, together with thalidomide administered at doses of 50–400 mg daily without interruption (Kulke et al. 2006). The overall objective radiologic response rate among patients receiving temozolomide and thalidomide in this study was 25%, a rate that is comparable with prior studies of both DTIC- and streptozocin-based chemotherapy in patients with neuroendocrine tumors (Engstrom et al. 1984, Bukowski et al. 1987, 1994). Neuropathy is a known toxicity related to thalidomide and occurred in 38% of the patient population. Grade 3 or 4 lymphopenia developed in 69% of the patients. Three of those patients were on the regimen for more than 6 months and developed opportunistic infections, leading to the recommendation that subsequent patients receive prophylaxis with trimethoprim-sulfamethoxazole.

Other chemotherapeutic agents have, to date, proved relatively inactive in neuroendocrine tumors. High-dose paclitaxel, administered with granulocyte colony-stimulating factor, was evaluated in 24 patients with metastatic carcinoid and islet cell tumors (Ansell et al. 2001). Significant hematologic toxicity was observed, and the objective radiologic response rate was only 8%. Treatment with docetaxel was associated with biochemical responses but no radiologic responses in a recent phase II trial of 21 patients with carcinoid tumors (Kulke et al. 2004a). No responses were observed in 18 neuroendocrine tumor patients treated with gemcitabine (Kulke et al. 2004b).

Novel treatment approaches for metastatic neuroendocrine tumors

The modest efficacy of current systemic treatment regimens has led to interest in the development of novel therapeutic approaches for patients with advanced neuroendocrine tumors. Such approaches include the use of targeted radiotherapy, as well as regimens incorporating inhibitors of growth factor signaling pathways.

Somatostatin receptor targeted radiotherapy

Traditional external beam radiation therapy is beneficial in patients with neuroendocrine tumor metastases to bone, but has little utility for more common visceral metastases. A more broadly applicable strategy includes the therapeutic use of radio-labeled somatostatin analogs (McCarthy et al. 1998, Meyers et al. 2000, Anthony et al. 2002, Paganelli et al. 2002, Waldherr et al. 2002, Buscombe et al. 2003, Kouvaraki et al. 2003, 2005). Scintigraphy with Indium-111-labelled octreotide has been commonly used to localize previously undetected primary or metastatic neuroendocrine tumor lesions. At higher doses, Indium-111-labelled octreotide has also been evaluated as a potential novel therapeutic. Unfortunately, objective response rates with this agent have been low (DeJong et al. 2002). More encouraging results have been obtained with octreotide coupled to Yttrium-90, a high-energy β-particle emitter. In early phase II trials, objective radiologic responses were noted in up to 23% of patients with metastatic neuroendocrine tumors (Virgolini et al. 2002, Waldherr et al. 2002). The longer-term utility of this agent, however, appears to be limited by both renal and hematologic toxicity (Valkema et al. 2005).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>Tumor response rate (%)</th>
<th>Median overall, survival (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorozotocin</td>
<td>33</td>
<td>30</td>
<td>18.0</td>
<td>Moertel et al. (1992)</td>
</tr>
<tr>
<td>Fluorouracil + streptozocin</td>
<td>33</td>
<td>45</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin + streptozocin</td>
<td>36</td>
<td>69</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>DTIC</td>
<td>50</td>
<td>34</td>
<td>19.3</td>
<td>Ramanathan et al. (2001)</td>
</tr>
<tr>
<td>Temozolomide + thalidomide</td>
<td>11</td>
<td>45</td>
<td>NR</td>
<td>Kulke et al. (2006)</td>
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<tr>
<td>Retrospective studies</td>
<td></td>
<td></td>
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<tr>
<td>Doxorubicin + streptozocin</td>
<td>16</td>
<td>6</td>
<td>NR</td>
<td>Cheng &amp; Saltz (1999)</td>
</tr>
<tr>
<td>Doxorubicin + streptozocin</td>
<td>16</td>
<td>6</td>
<td>20.2</td>
<td>McCollum et al. (2004)</td>
</tr>
<tr>
<td>Steptozocin + doxorubicin + fluorouracil</td>
<td>84</td>
<td>39</td>
<td>37</td>
<td>Kouvaraki et al. (2004)</td>
</tr>
</tbody>
</table>

DTIC, dacarbazine; NR, not reported.

aNumber of patients evaluable for efficacy endpoints.

bIncludes patients with locally advanced disease.

Table 2 Selected trials of systemic chemotherapy for metastatic pancreatic endocrine tumors

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Most recently, octreotide labeled with lutetium ($^{177}$Lu), a low-energy β-particle emitter, has been evaluated in a phase I study, with encouraging results. In one series, 131 patients with somatostatin receptor-positive, advanced neuroendocrine tumors received $^{177}$Lu-octreotate administered every 6–10 weeks, to a final intended dose of 600–800 mCi (Kwekkeboom et al. 2005). There were 35 objective responses (27%), three of which were complete.

**Inhibition of VEGF and other growth factor signaling pathways**

Gastrointestinal neuroendocrine tumors overexpress several growth factors, including VEGF, basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-α and -β, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF-I). In addition, expression of several growth factor receptors, such as PDGF receptor (PDGFR), IGF-I receptor (IGF-IR), epidermal growth factor receptor (EGFR), VEGF receptor (VEGFR), and stem cell factor receptor (KIT) has been observed (Chaudhry et al. 1992, 1993, 1994, Christofori et al. 1995, Nilsson et al. 1995, Krishnamurthy & Dayal 1997, Ambs et al. 1998, Terris et al. 1998, La Rosa et al. 2003, Lankat-Buttgereit et al. 2005, Hopfner et al. 2006). Disruption of several of these signaling pathways in different experimental models has resulted in inhibition of neuroendocrine cell growth, leading to a number of recent clinical trials with receptor tyrosine kinase inhibitors and monoclonal antibodies targeting growth factor signaling in patients with advanced neuroendocrine tumors (Table 3).

Imatinib mesylate inhibits the Bcr-Abl, PDGFR-α and -β, and KIT tyrosine kinases. In preclinical studies, incubation of neuroendocrine tumor cells in the presence of imatinib resulted in decreased cell growth (Lankat-Buttgereit et al. 2005). In a phase II study, however, the administration of imatinib to 27 patients with advanced neuroendocrine carcinoid tumors resulted in only one objective response (Yao et al. 2007). Similarly, while exposure to gefitinib, a tyrosine kinase inhibitor targeting the EGFR, resulted in growth inhibition of neuroendocrine cell lines, few responses were reported when gefitinib was administered to patients with neuroendocrine tumors in a phase II study (Hopfner et al. 2003, Hobday et al. 2006).

Neuroendocrine tumors have long been known to be highly vascular, and preliminary results from clinical trials of VEGF pathway inhibitors in patients with advanced neuroendocrine tumors have been more encouraging. These studies suggest that inhibition of either VEGF or VEGFR has the potential for tumor growth inhibition, and in some cases, tumor regression.

### Table 3 Trials of novel targeted therapies in neuroendocrine tumors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecular target(s)</th>
<th>Patients</th>
<th>Tumor type</th>
<th>Tumor response rate (%)</th>
<th>Median TTP or PFS (weeks)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>18</td>
<td>Carcinoid</td>
<td>17</td>
<td>NR</td>
<td>Yao et al. (2005)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR-1, -2, -3; PDGFR-α, -β; KIT; RET; CSF-1R; FLT3</td>
<td>41</td>
<td>Carcinoid</td>
<td>2</td>
<td>44 (TTP)</td>
<td>Kulke et al. (2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66</td>
<td>Pancreatic</td>
<td>17</td>
<td>33 (TTP)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>40</td>
<td>Carcinoid</td>
<td>3</td>
<td>NR</td>
<td>Hobday et al. (2006)</td>
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<tr>
<td></td>
<td></td>
<td>31</td>
<td>Pancreatic</td>
<td>3</td>
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<td></td>
<td>mTOR</td>
<td>18</td>
<td>Carcinoid</td>
<td>11</td>
<td>NR</td>
<td>Yao et al. (2006)</td>
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<td></td>
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<td>13</td>
<td>Pancreatic</td>
<td>11</td>
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<td>endocrine</td>
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<tr>
<td>Temsirolimus</td>
<td>mTOR</td>
<td>21</td>
<td>Carcinoid</td>
<td>5</td>
<td>NR</td>
<td>Duran et al. (2006)</td>
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<tr>
<td></td>
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<td>15</td>
<td>Pancreatic</td>
<td>5</td>
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<tr>
<td>Imatinib</td>
<td>PDGFR-α, -β; KIT; Bcr-Abl</td>
<td>27</td>
<td>Carcinoid</td>
<td>4</td>
<td>24 (PFS)</td>
<td>Yao et al. (2007)</td>
</tr>
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</table>

CSF-1R, colony-stimulating factor receptor; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase-3; KIT, stem cell factor receptor; mTOR, mammalian target of rapamycin; NR, not reported; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RET, REarranged during transfection or glial cell-line derived neurotrophic factor; TTP, time to progression; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

aNumber of patients evaluable for efficacy endpoints.

bPatients also received treatment with octreotide.
In one phase II trial, 44 patients with advanced or metastatic carcinoid tumors on a stable dose of octreotide were randomly assigned to receive either bevacizumab (15 mg/kg), a humanized monoclonal antibody targeting VEGF, or pegylated IFN-α-2b (0.5 µg/kg; Yao et al. 2005). Four out of twenty-two patients (18%) treated with bevacizumab achieved confirmed radiographic partial responses, when compared with none of the patients who received pegylated IFN-α-2b. After 18 weeks, 96% of patients treated with bevacizumab remained progression-free, when compared with 68% of patients treated with IFN-α-2b. Hypertension was the most common grade 3/4 adverse event observed with bevacizumab, and granulocytopenia and fatigue were commonly associated with pegylated IFN-α-2b.

Sunitinib, a multitargeted tyrosine kinase inhibitor with activity against not only VEGFR-1, -2, and -3, but also PDGFR-α and -β, KIT, RET, FMS-like tyrosine kinase-3 (FLT3), and colony-stimulating factor receptor (CSF-1R), has also recently been shown to have activity in patients with advanced neuroendocrine tumors. A phase I study of sunitinib included four patients with neuroendocrine tumors; out of these patients, one achieved an objective radiologic response, and a second achieved a minor response with prolonged stable disease. The 28 patients in this study received doses between 15 and 59 mg/m², ranging from 50 mg every other day to 150 mg/day (Faivre et al. 2006). These observations led to further evaluation of sunitinib in a phase II study, in which 109 patients with advanced neuroendocrine tumors received repeated 6-week treatment cycles of sunitinib, administered at an oral dose of 50 mg once daily for 4 weeks, followed by 2 weeks off treatment (Kulke et al. 2005). Hematologic toxicities were relatively uncommon, with grade 3 or 4 neutropenia or thrombocytopenia reported in 21 and 10% of patients respectively. The most common grade 3 or 4 non-hematologic adverse events were fatigue (27%), abdominal pain (12%), and hypertension (11%). A total of 11 out of 66 (17%) patients with pancreatic endocrine tumors and one of 41 (2%) patients with carcinoid tumors achieved confirmed partial responses. The median duration of response was 37 weeks in patients with carcinoid tumors and had not been reached in patients with pancreatic tumors. Stable disease was observed in 83% of the patients with carcinoid tumors and 68% of those with pancreatic endocrine tumors. The median time to tumor progression was 44, 33, and 40 weeks for patients with carcinoid tumors, pancreatic endocrine tumors, and for the entire cohort respectively. Based on these results, further evaluation of sunitinib in patients with advanced neuroendocrine tumors is planned.

Inhibition of mammalian target of rapamycin (mTOR)

mTOR is a threonine kinase that mediates downstream signaling from a number of pathways, including the VEGF and IGF signaling pathways implicated in neuroendocrine tumor growth (Vignot et al. 2005). Activation of the PI3K/AKT/mTOR pathway has been shown to cause increased translation of proteins regulating cell cycle progression, and inhibitors of mTOR have recently shown promising early activity in a number of cancer types (Smolewski 2006). In one phase II study, 37 patients with progressive neuroendocrine tumors were treated with the mTOR inhibitor temsirolimus. The objective overall response rate was 5.6%, with 63.9% of patients experiencing either partial response or stable disease; in this study, higher baseline tumor levels of mTOR predicted for better outcomes (Duran et al. 2006). In a second phase II study, 32 patients with neuroendocrine tumors were treated with a combination of the mTOR inhibitor RAD001 (everolimus; 5 mg/day) and depot octreotide (30 mg every 4 weeks; Yao et al. 2006). In a preliminary report, partial responses (by RECIST) were observed in 2 out of 17 (12%) carcinoid tumor patients and 2 out of 13 (15%) patients with pancreatic neuroendocrine tumors. Further trials to confirm the activity of mTOR inhibitors, either administered alone or in combination with other agents, are planned.

Conclusions

The development of novel, targeted agents is of particular interest in neuroendocrine tumors, in which traditional treatment modalities have had only limited success. Promising recent approaches include somatostatin receptor-targeted radiotherapy, inhibition of mTOR, and inhibition of the VEGF signaling pathway. Even with these novel agents, however, response rates, as measured by traditional response criteria, remain low. It is possible that many of these agents also have a cytostatic effect. However, the indolent nature of neuroendocrine tumors, while beneficial from the standpoint of the patient, makes it difficult or impossible to determine from phase II studies whether stable disease reflects drug effect or simply the natural history of the disease. For similar reasons, the prolonged survival times of patients with advanced neuroendocrine tumors, together with varying selection criteria in trials, make the evaluation of survival data in these studies challenging. Randomized trials or, alternatively, the development of surrogate endpoints
of response, including the validation of biochemical, may expedite the more definitive evaluation of these potentially promising agents for neuroendocrine tumors.

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References


Smollewski P 2006 Recent developments in targeting the mammalian target of rapamycin (mTOR) kinase pathway. *Anticancer Drugs* 17 487–494.


Thorson A, Biorck G, Bjorkman G & Waldenstrom J 1954 Malignant carcinoid of the small intestine with metastases to the liver, valvular disease on the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. *American Heart Journal* 47 795–817.


