

# Treatment of advanced disease in patients with well-differentiated neuroendocrine tumors

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## SUMMARY

Well-differentiated neuroendocrine tumors (NETs), which are also referred to as well-differentiated endocrine carcinoma according to WHO terminology, are usually slow-growing cancers, even when they exhibit gross local invasion and/or metastases. The survival of patients with metastatic NET is often measured in years to decades. Once NET progresses or becomes symptomatic the patient's prognosis is poor. An important challenge for clinicians is to distinguish at an early stage those patients who will die with the disease, from those who will succumb because of it, so that the appropriate level of care can be administered. Reliable genomic predictors could provide substantial advancements in prognosis and, possibly, treatment; however, such markers are currently unavailable. Early literature on the treatment of NETs is confounded by a lack of formal objective response criteria. Somatostatin analogs can control symptoms and can stabilize some slow-growing tumors, but rarely result in tumor regression. Surgery is curative in only a minority of patients, and systemic chemotherapy is minimally effective. Advances in the understanding of tumor biology have led to the identification of important cellular processes involved in the pathogenesis of NETs, and agents that target these processes have now entered clinical trials. We will discuss the data on therapies currently used to treat well-differentiated NETs, and the strategies being used in clinical trials.

**KEYWORDS** hepatic embolization, mTOR, neuroendocrine tumors, somatostatin, VEGF

## REVIEW CRITERIA

Information for this Review was compiled by searching the PubMed and MEDLINE databases for articles published until 20 April 2008. Only articles published in English were considered. The search terms used included "neuroendocrine tumor" in association with the search terms: "metastatic", "clinical trial", "islet cell carcinomas", "carcinoid tumors", "targeted therapy", "cytotoxic therapy", and "prognosis". Full articles were obtained and references were checked for additional material when appropriate.

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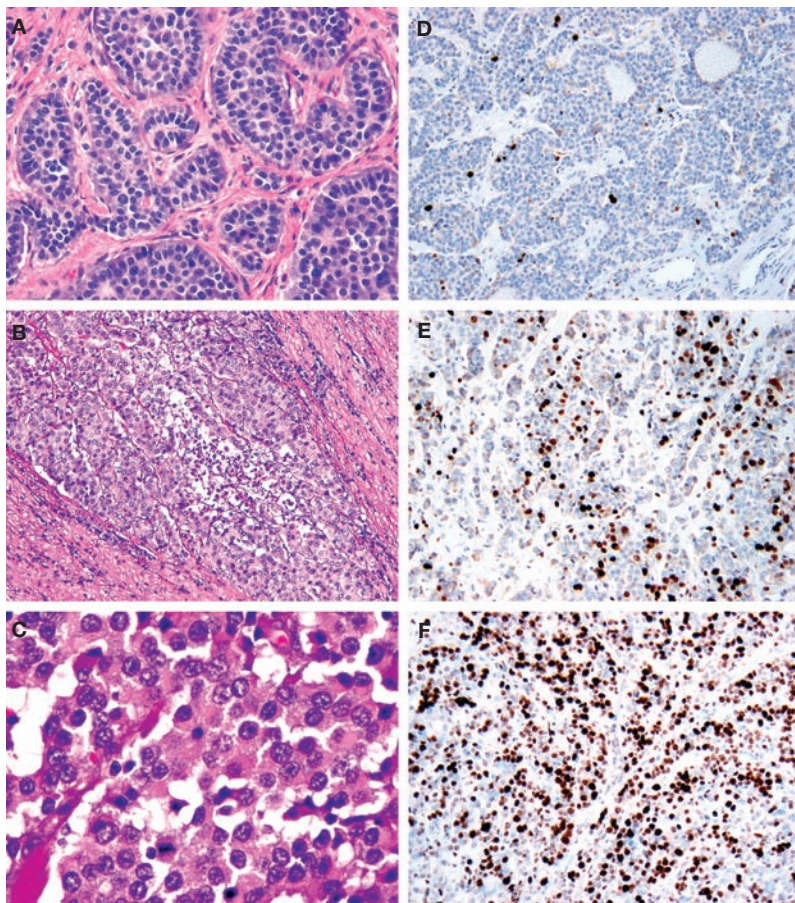
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## INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are rare neoplasms that arise from the diffuse neuroendocrine cell system. Tumors that develop from the neuroendocrine tissues of the aerodigestive tract are called carcinoid tumors, whereas tumors of the endocrine tissues of the pancreas (i.e. islets of Langerhans) are known as pancreatic endocrine tumors (PETs) or islet-cell carcinomas. This family of well-differentiated neoplasms (i.e. carcinoid tumors and PETs) is morphologically and clinically distinct from high-grade neuroendocrine carcinoma. This latter entity is closely related to pulmonary small-cell carcinoma, is highly aggressive, and is generally managed with platinum-based chemotherapy.<sup>1</sup> Well-differentiated and poorly differentiated NETs are grouped together only because of generic neuroendocrine marker expression (i.e. expression of the markers synaptophysin and chromogranin detected by immunohistochemistry). The biology and clinical outcome of poorly differentiated NETs, however, are vastly different from those of well-differentiated NETs. In fact, our investigations suggest that poorly differentiated neuroendocrine carcinomas are likely to possess a non-neuroendocrine cell lineage and are more closely related to a *de novo* carcinoma (L Tang, unpublished data). The so-called neuroendocrine carcinoma stem cell is thought to be the enterochromaffin intestinal cell found in the intestinal crypts.<sup>2</sup>

Well-differentiated NETs exhibit diverse clinical outcomes, which can sometimes be stratified by certain histopathological features including cytological grade degree, angioinvasion, proliferative index (as assessed by mitotic index and Ki67), tumor size, presence of metastases, and functional activity.<sup>3</sup> As with most tumors, although advanced tumor stage is indicative of an unfavorable prognosis, prediction of the clinical outcome of low-grade NETs on the basis of traditional histopathology alone has been unsatisfactory. In some studies, however, tumor grade has been correlated with survival (Figure 1).<sup>4,5</sup> The WHO



**Figure 1** Grading of neuroendocrine tumors (NETs). A typical well-differentiated NET exhibits a nested growth pattern with uniform nuclei, no significant cytological atypia and no mitotic activity (**A**). An intermediate or high-grade NET evinces punctate tumor necrosis (**B**), with increased mitotic activity (**C**). Ki67 immunoreactivity (nuclear staining), used to estimate the proliferative index of NETs, is usually <2–5% in a well-differentiated or low-grade NET (**D**), is gradually increased in an intermediate grade NET (**E**), and may reach >75% in a high-grade tumor (**F**).

classification incorporates both tumor stage and tumor grade into each prognostic group. One hypothetical proposal of TNM classification provides a simple and practical system for risk stratification of patients.<sup>6</sup> Included in the TNM classification is an additional grading system (G1, G2 and G3) based on tumor mitotic activity and the proliferative index of the tumor (Ki67 index). Additional clinical data are required to validate this classification system. Notably, this grading system is not considered or incorporated in any of the clinical trials cited herein, which makes comparisons of the data extremely difficult.

Most patients with NET, especially those with tumors that are unresponsive to hormones (i.e. hormonally nonfunctional), present with

metastatic disease. Inoperable disease is often followed expectantly, or is managed with hormonal therapy, because such tumors are typically slow-growing, and patients without hormonal symptoms are often asymptomatic. About half of NETs are hormonally nonfunctional, meaning that they do not produce a hormone that causes a clinical syndrome. Functional NETs can secrete a variety of hormones that lead to different clinical syndromes. Often these syndromes can be managed effectively with somatostatin analogs. Typical indications for therapy are pain or symptoms due to tumor bulk, symptoms due to uncontrolled, dysregulated hormone secretion, significant tumor burden or progression of disease under observation. Once the NET progresses or is symptomatic despite somatostatin analog treatment, therapeutic options are extremely limited and no therapy at this time can be considered standard. This Review will focus on the management of advanced NETs as defined above.

#### RESECTABLE PRIMARY DISEASE

Some subsets of NETs can be benign in nature, such as focal adenomas, which can generate a hormonal syndrome. Such tumors are cured by primary resection. The treatment of a localized, primary, malignant NET is definitive surgical resection, although most patients will have metastatic disease at presentation (Figure 2). Before embarking on surgery, a careful work-up to determine the extent of disease is warranted to rule out metastatic disease. No evidence supports the use of adjuvant therapy of any sort (i.e. hormonal therapy, chemotherapy, or radiation therapy) for the treatment of either resected NET or carcinoid tumors.

#### LIVER-SPECIFIC DISEASE: ROLES OF TUMOR RESECTION OR EMBOLIZATION

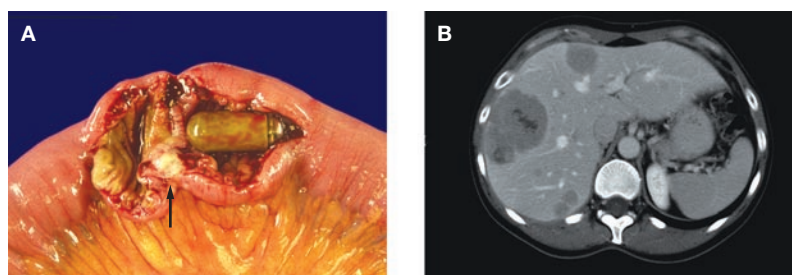
Apart from local-regional lymph-node metastases, most carcinoid and islet-cell carcinomas demonstrate a remarkable tropism for the liver (Figure 3). For this reason, hepatic resection, radiofrequency ablation, and hepatic arterial embolization (HAE) have been used to control tumor burden. For those patients in whom all hepatic metastases seem to be resectable, and in whom no extrahepatic disease is observed, resection should be considered. Radiofrequency ablation can also be used to control small-volume metastatic disease. Most patients, however, will present with bulky disease and will not be

candidates for such a procedure. In general, 'debulking surgery' is not routinely indicated if a complete resection is not possible. If a particular dominant metastasis is considered to be the primary cause of symptoms because of tumor bulk, or if hormonal symptoms are refractory to medical management, some retrospective series suggest that long-term symptomatic relief can be obtained with surgical debulking.<sup>7–10</sup> Selection bias and the lack of randomized data confound quantitative interpretation of reported results. Nevertheless, resection might be considered in carefully selected patients.

The rationale for HAE is on the basis of the dual blood supply of the liver; tumors receive the majority of their blood supply via the hepatic artery, whereas the normal hepatic parenchyma receives about three-quarters of its blood supply through the portal vein. Thus, occlusion of the hepatic arterial supply can result in selective ischemia and necrosis of the tumor relative to the normal liver around it. Selective HAE, with or without concurrent hepatic arterial infusion of chemotherapy ('chemoembolization'), is frequently employed as a palliative technique in patients with symptomatic hepatic metastases who are not candidates for surgical resection.<sup>11,12</sup> Duration of response is highly variable and might be as brief as 4 months or as long as 2 years, which again reflects the differences in tumor biology.<sup>13,14</sup> The potential complications of HAE are not trivial and include, but are not limited to, the development of bleeding, pain, infection, arterial thrombotic events and an approximate 3–5% treatment-related mortality rate.<sup>15</sup> In addition, no adequately powered, controlled studies have compared HAE to any other therapies. Nonetheless, HAE has become accepted as one standard, palliative option for patients with unresectable NETs who have liver-only or liver-dominant metastases.

#### IMAGING THE SOMATOSTATIN RECEPTOR BY SOMATOSTATIN SCINTIGRAPHY

Scintigraphy was first developed in the early 1990s, and octreotide labeled with indium 111 (<sup>111</sup>In pentetreotide, OctreoScan® Mallinckrodt, Inc, St Louis, MO) was successfully used to localize previously undetected primary or metastatic lesions.<sup>16</sup> Although this technique is often used for this purpose, the incidence of tumors that are undetected by modern CT and MRI, and then detected by <sup>111</sup>In pentetreotide scintigraphy, in order to change a patient's therapy, is really



**Figure 2** Typical presentation of an ileal carcinoid tumor. A subcentimeter carcinoid tumor (arrow) was detected by capsular endoscopy, where it blocked the capsule from passing through the small bowel lumen and caused partial obstruction symptoms (A). The liver, on the other hand, had multiple metastatic carcinoid tumors which measured up to 8.0 cm (B).



**Figure 3** A patient with a metastatic nonfunctional carcinoid tumor, Eastern Cooperative Oncology Group performance status 0, with bulky liver disease, which illustrates the tropism of NETs for the liver.

quite low.<sup>17–19</sup> Somatostatin-analog scintigraphy is now used to assess relevant somatostatin receptor expression *in vivo* in tumor samples from patients, to predict who should be considered for somatostatin-analog therapy. A report in 2008 demonstrated that somatostatin receptor subtype 2 expression by <sup>111</sup>In pentetreotide scintigraphy correlated with both tracer uptake and an improved prognosis.<sup>20</sup> Patients with negative somatostatin scintigraphy scans should not be placed on somatostatin analogs. This contraindication is particularly important in the treatment of insulinomas, as there are five types of somatostatin receptors and octreotide binds only to type 2, and to a lesser extent, to type 5 receptors. Administration of somatostatin to a

patient with an insulinoma whose tumor does not bind octreotide could lead to a blunting of the compensatory glucagon response, and might actually worsen hypoglycemia.

Somatostatin-analog scintigraphy has not been evaluated for the assessment of treatment response in patients. CT or MRI would be more suitable tests in this clinical situation. As NETs are often isodense with normal hepatic parenchyma, routine CT scans are of somewhat limited value. MRI or triphasic CT might be more appropriate techniques for imaging these tumors.

## SYSTEMIC TREATMENT

### The somatostatin analogs

Somatostatin is a peptide (i.e. 14 amino acids in length) that regulates the secretion of several hormones, including growth hormone, insulin, glucagon and gastrin.<sup>21</sup> Approximately 80% of carcinoid tumors express the somatostatin receptor.<sup>22</sup> Octreotide is a synthetic analog of somatostatin (i.e. eight amino acids in length), which was designed to bind with the somatostatin receptor, but to have a longer half-life than somatostatin. A depot, long-acting, release preparation has been developed, and a once-monthly intramuscular injection of this agent is now the most common form of octreotide administration.<sup>23–25</sup> Demonstration of stabilization of disease has been reported in some patients with progressive disease when treated with octreotide or a similar drug, lanreotide.<sup>26,27</sup> Tumor regression, however, is extremely rare and occurs in less than 5% of somatostatin-analog-treated patients.<sup>28–31</sup> These agents are highly effective in treating hormonally induced NET symptoms.

### Interferon- $\alpha$

Initial reports on the use of interferon- $\alpha$  (IFN- $\alpha$ ) in patients with NET reported combined biologic response (i.e. a decrease in hormone production) with objective response (i.e. tumor shrinkage), which produced very high 'response' rates. In this early literature, a subjective improvement in physical examination findings was often accepted as satisfactory evidence of response—criteria that would not be accepted today. A subsequent trial from the Mayo clinic, that administered 9 million units of IFN- $\alpha$  three times per week, showed a high degree of toxicity and minimal evidence of activity. The authors concluded that IFN- $\alpha$  did not have a role in the treatment of NETs.<sup>32</sup> A trial that combined the use of IFN- $\alpha$  with 5-fluorouracil (5-FU) showed only modest

activity that was similar to that expected from 5-FU alone.<sup>33</sup> A review of the available studies by Plöckinger and Wiedenmann in 2007 estimated that approximately 10% of patients achieved some degree, however modest, of actual tumor regression. Major objective responses are essentially anecdotal.<sup>34</sup> Although IFN- $\alpha$  may have an antiproliferative effect, as shown by disease stabilization, the adverse effects (e.g. including fatigue, fever and anorexia) often outweigh the benefits, and these adverse effects should be considered carefully before using these agents.<sup>35,36</sup>

### Conventional chemotherapy

At the present time conventional chemotherapy has no clearly defined role in the treatment of metastatic NETs, and no regimen constitutes a clearly defined standard of care. Early literature indicated high response rates to some chemotherapy agents, especially in patients with PETs, although many of these studies are not reliable and lack modern standards of response assessment. A lack of formal criteria for defining an objective response, and the frequent use of such unreliable measures as perceived changes in physical examination findings or a drop in hormone level as the basis for declaring a major objective response are, in part, the reasons for a wide range of reported responses. As such, any standard recommendations based on these studies must be made with extreme caution. Subsequent data, albeit retrospective, suggest that islet-cell carcinomas seem to be more responsive to chemotherapy than NETs.

## CHEMOTHERAPY FOR THE TREATMENT OF ISLET-CELL TUMORS

Streptozotocin is an antibiotic that induces diabetes in animals by destroying pancreatic beta cells.<sup>37</sup> This observation led to studies in patients with NETs, which showed that those with insulinoma tumors had a decrease in hypoglycemia with streptozotocin.<sup>38</sup> Other studies and case reports with similar responses and complete remissions were noted.<sup>39,40</sup> This effect prompted studies on its combination with other cytotoxic drugs. A publication in 1980 indicated a high response rate for patients with islet-cell tumors treated with the combination of streptozotocin plus 5-FU.<sup>41</sup> In a follow-up study, the Eastern Cooperative Oncology Group (ECOG) randomly allocated 105 patients with advanced islet-cell carcinomas to streptozotocin plus doxorubicin hydrochloride, streptozotocin plus 5-FU or chlorozotocin alone.

The reported response rate was a remarkable 69% for the streptozotocin and doxorubicin hydrochloride combination, 33% for streptozotocin and 5-FU, and 30% for chlorozotocin alone.<sup>42</sup> This report led to the widespread impression that islet-cell tumors were highly responsive to chemotherapy. Clinical experience, however, suggested otherwise. In a retrospective review of 16 consecutive patients with islet-cell tumors treated with streptozotocin and doxorubicin hydrochloride, Cheng and Saltz<sup>43</sup> reported that only one patient had a major response, and the others showed no tumor shrinkage. Analysis of the methods section of the paper that reported the 69% response rate indicated that ‘response’ was defined as a 50% tumor reduction by CT scan or liver–spleen scan, a 30% decrease in liver span on physical examination, or a 50% reduction of a hormone, with no report of how many patients actually had CT-documented regressions.<sup>42,43</sup> The 69% response rate is now acknowledged, therefore, to be a gross overstatement of the degree of activity that can be expected from streptozotocin-based therapy. Other studies have reported lower response rates that range from 6% to 39%.<sup>44,45</sup> A retrospective review examined the objective tumor response rate and duration of progression-free survival in 84 patients with locally advanced or metastatic pancreatic islet-cell carcinoma treated with the combination of 5-FU, streptozotocin and doxorubicin hydrochloride. The overall response rate was 39%, as measured by RECIST (Response Evaluation Criteria in Solid Tumors), and one patient reportedly achieved a complete response. Median time between the first cycle of chemotherapy and tumor response was 3.9 months, which suggests that islet-cell carcinoma might respond slowly to chemotherapy.<sup>45</sup> A second retrospective review examined the role of 5-FU, folinic acid (the infusional de Gramont regimen) plus streptozotocin. Of the 15 evaluable patients, 1 patient had a complete response and 7 patients had a partial response with no grade 3–4 toxicities observed, as assessed using the WHO criteria.<sup>46</sup> The small sample size and retrospective nature of this study makes it difficult to draw definitive conclusions.

#### CHEMOTHERAPY FOR CARCINOID TUMORS

The role of streptozotocin plus either 5-FU or cyclophosphamide was tested in an ECOG study of 118 patients with metastatic carcinoid tumors; response rates for the two groups were similar (33% and 26%, respectively), with no difference

in overall survival. However, significant nausea and renal toxicity were encountered, which were considered to be prohibitive.<sup>47</sup> In the streptozotocin plus cyclophosphamide group 53 of 57 patients (93%) experienced nausea (in 33 of whom it was described as “moderate–severe”), and 84% of patients in the streptozotocin plus 5-FU group experienced nausea (in 20 of 49 patients it was “moderate–severe”). Renal toxicity, defined by a rise in serum creatinine level, occurred in about 25% of patients in both groups, with two renal-failure-related deaths thought to be from streptozotocin. Leukopenia and thrombocytopenia were noted (50% and 20%, respectively, defined as grade 2 in both groups). A subsequent ECOG trial attempted to decrease toxicity, and compared streptozotocin plus 5-FU to doxorubicin hydrochloride alone. Although treatment in both groups was better tolerated than seen in the earlier ECOG study, the response rate to streptozotocin plus 5-FU was similar to that of doxorubicin hydrochloride alone (22% and 21%, respectively), and no difference in overall survival was noted.<sup>48</sup> The Southwest Oncology Group (SWOG) evaluated a four-drug combination of 5-FU, doxorubicin hydrochloride, cyclophosphamide and streptozotocin in 56 patients with advanced carcinoid tumors. The reported objective response rate was approximately 30% (similar to other trials of combination streptozotocin and 5-FU), with a median overall survival of only 11 months.<sup>49</sup> Again, the definition of response in these trials would not meet today’s standards, and even the modest degree of activity reported is probably a substantial overestimation. In 2005, a phase II–III ECOG trial of 250 patients who received doxorubicin hydrochloride plus 5-FU versus streptozotocin plus 5-FU in the treatment of advanced carcinoid tumors was reported.<sup>50</sup> The response rates were 16% in both groups, with a modest survival advantage for patients in the streptozotocin plus 5-FU group (24.3 vs 15.7 months) but with substantial adverse effects as a result of this treatment. A third of patients who received streptozotocin developed renal toxicity. These trials fail to demonstrate a meaningful benefit of combination therapy over single-agent therapy in the treatment of NETs and, in the authors’ opinion, combination therapy should not be routinely offered for patients with carcinoid tumors.

Dacarbazine and the related oral compound temozolomide are alkylating agents that might

be active in a subset of patients with NET. As with other chemotherapy agents these drugs seem to be more active in pancreatic islet-cell tumors than in carcinoid tumors. In an ECOG phase II study of dacarbazine, 14 of the 42 patients (33%) with islet-cell pancreatic carcinoma were reported to have had a partial or complete response.<sup>51</sup> A SWOG study reported a response rate of 16% in 9 of 56 patients with metastatic carcinoid tumors who received dacarbazine therapy. Again, methodologic differences between these studies and the lack of clearly defined response criteria make it difficult to interpret these results.<sup>52</sup> In the phase II–III ECOG trial of 250 patients noted above, participants were given dacarbazine after progression on streptozotocin-based therapy, with a modest overall response rate of 8%.<sup>50</sup> Toxicity was considerable in both studies with two deaths reported in the ECOG study.

In another phase II study that used modern response criteria, Kulke *et al.*<sup>53</sup> tested the combination of temozolomide and thalidomide in 29 patients with metastatic NETs. Patients received temozolomide at a dose of 150 mg/m<sup>2</sup> for 7 days every 2 weeks plus daily thalidomide (dose range 50–400 mg). The overall response rate was approximately 25% (a 45% response rate in patients with pancreatic NETs, and a 7% response rate in those with carcinoid tumors), which again suggests that pancreatic islet-cell tumors are more sensitive to chemotherapy than carcinoid tumors. In total, 55% of patients discontinued therapy because of treatment-related toxicity. Moreover, 38% of patients developed significant neuropathy, a known adverse effect of thalidomide. Grade 3–4 lymphopenia was noted in 70% of patients; 10% of these patients developed opportunistic infections, which is a known adverse effect of temozolomide. A retrospective review showed that temozolomide was active in approximately 14% of patients, while in a single phase II study of 18 patients with NETs (13 carcinoid, 5 islet-cell tumors) thalidomide showed no antitumor activity.<sup>54,55</sup> These findings suggest that the active drug in this combination is probably temozolomide. Whether a meaningful difference exists between the activity of temozolomide and dacarbazine is difficult to establish, as no trials have compared these two agents.

Kulke *et al.*<sup>56</sup> retrospectively assessed 76 patients who received treatment with temozolomide and thalidomide from the above study (30 patients), or patients treated with the combination of

temozolomide and bevacizumab (46 patients). A radiographic response (defined by RECIST) was seen in approximately 11 of 35 patients (33%) with pancreatic NETs, but in none of 38 patients with carcinoid tumors ( $P < 0.001$ ). In 21 available specimens, complete absence of O-6-methylguanine-DNA methyltransferase (MGMT) expression seemed to define patients with pancreatic NET who achieved significant benefit from temozolomide (5 of 8 pancreatic NET and none of 13 carcinoid tumors), which indicated that the success of treatment with temozolomide might depend on the absence of MGMT expression. A reasonable conjecture is that the same predictive ability of MGMT expression could hold true for dacarbazine therapy as well, since the mechanisms of action of these two agents are essentially the same.

Overall, on the basis of the modest response rates and nontrivial toxicities, systemic chemotherapy rarely has a role in the early management of metastatic, low-grade NETs, and is usually reserved for patients with symptoms owing to tumor bulk or uncontrolled hormonal excess, or patients with substantial and/or rapid progression under observation.

## EMERGING THERAPIES

Described below are some of the published trials of emerging therapies for the treatment of NETs, some of which have only been published in abstract form and/or are the results of phase II trials. They constitute preliminary data, therefore, and cannot be considered as standard management strategies.

### Radiolabeled somatostatin-analog therapy

In single-center trials, radionuclide-labeled somatostatin-analog therapy for patients with advanced, unresectable, <sup>111</sup>In pentetreotide-positive NET has been reported to have some efficacy with acceptable toxicity. Several radioisotopes linked to a somatostatin analog have been used and include <sup>111</sup>In, yttrium-90 (<sup>90</sup>Y), and lutetium-177 (<sup>177</sup>Lu). Studies of the <sup>90</sup>Y-labeled somatostatin analog (a high-energy  $\beta$ -particle emitter) reported response rates of up to 27%.<sup>57,58</sup> A European multicenter trial known as MAURITIUS (Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative) used <sup>90</sup>Y-lanreotide to evaluate 39 patients with NETs. Minor tumor regressions were seen in 20% of patients, and 44% of patients achieved stable disease.<sup>59</sup> To what degree some of these patients

might have had stable disease as a consequence of the natural history of their tumor is not clear. Adverse effects associated with  $^{90}\text{Y}$ -octreotide include renal and hematologic toxicities.<sup>60</sup>

An analysis of 504 patients with metastatic NETs who received  $^{177}\text{Lu}$ -octreotate was reported in 2008.<sup>61,62</sup> Complete remission occurred in 2% of patients, partial remission in 28% of patients, and minor remission (decrease in tumor bulk of 25–50%) in 16% of patients. Only 20% of patients had progression of disease 3 months after administration of  $^{177}\text{Lu}$ -octreotate. The median time to progression was approximately 40 months overall; however, only 43% of patients had documented disease progression before therapy was initiated. Serious toxicity was seen in three patients who developed myelodysplastic syndrome, and temporary, nonfatal, liver toxicity occurred in two patients. Radiolabeled somatostatin analogs might hold promise as an active treatment. The degree of activity and toxicity that patients can expect from this treatment has not yet been adequately defined, and this approach remains under investigation.

#### **Mammalian target of rapamycin inhibitors: temsirolimus and everolimus**

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that has a central role in the regulation of cellular function, and mediates downstream signaling from a number of signaling pathways, including VEGF and insulin-like growth factor (IGF). These signals have been implicated as critical pathways in NET growth. In a phase II trial, 36 patients with documented progression of disease (21 with carcinoid tumors, and 15 with islet-cell tumors) were treated with 25 mg intravenous weekly doses of temsirolimus (also known as CCI779) with an overall response rate of 5.6%.<sup>63</sup> This study is in contrast to a phase II trial of another mTOR inhibitor, everolimus (also known as RAD001) at either 5 mg or 10 mg, combined with 30 mg octreotide. In this study, 17% of patients had a partial response and 75% had stable disease. The most common grade 3 adverse effects, which occurred in approximately 10% of patients ( $n = 60$ ), included fatigue (6 patients), mucositis (5 patients) and diarrhea (6 patients). A 3% risk of pneumonitis was noted in the 10 mg group, which contrasts with the 19% risk of pneumonitis in the temsirolimus trial.<sup>63</sup> For patients who had documented progression of disease at study entry, the median progression-free survival was 38 weeks.<sup>64</sup>

#### **VEGF inhibitors**

Carcinoid tumors and other NETs are highly vascularized and extensively express VEGF.<sup>65,66</sup> Bevacizumab was tested in a phase II trial, in which 44 patients with advanced or metastatic NETs were randomly assigned to receive either bevacizumab (15 mg/kg every 3 weeks) or pegylated IFN- $\alpha$ 2b.<sup>67</sup> An 18% (4 of 22 patients) partial response rate was observed in the bevacizumab group compared with 0% in the IFN- $\alpha$ 2b group. At 18 weeks, 96% of the patients treated with bevacizumab remained free of disease progression compared with 68% of patients treated with IFN- $\alpha$ 2b. Grade 3 or 4 hypertension was 53%, much higher than the 11–21% that was reported in pivotal colon,<sup>68</sup> lung,<sup>69</sup> and breast cancer trials,<sup>70,71</sup> but easily controlled with antihypertensive medications. Importantly, 40% of patients in the bevacizumab group did not have documented disease progression at study entry.<sup>72</sup>

Sunitinib is an orally active, small, multitargeted agent that blocks the VEGF receptor as well as the platelet-derived growth factor receptor  $\beta$ , KIT and RET proteins. A phase II study included 109 patients with advanced NET who received 50 mg sunitinib for 4 weeks followed by a 2-week break. Of the patients with PET, 11 of 66 (17%) achieved a confirmed partial response compared with 1 patient of 41 (2%) with carcinoid tumors.<sup>73</sup> However, 25% of patients in both groups had grade 3 fatigue. Many such 'targeted' agents are now being investigated in phase III trials.

#### **FUTURE DIRECTIONS: IGF INHIBITORS**

NETs frequently express both IGFs and their receptors (IGFRs), and, as such, are potentially dependent on autocrine stimulation by this pathway for growth and survival.<sup>74,75</sup> The principal pathways for transduction of the IGF signal are the mitogen-activated protein kinase and phosphatidylinositol 3 kinase–Akt pathways.<sup>76</sup> In carcinoid tumor cell lines, exogenous IGF activates mTOR and increases cellular proliferation.<sup>77,78</sup> Studies in NET cell lines when cultured with an IGF inhibitor (NVP-AEW541) demonstrated apoptosis that was characterized by activation of the apoptotic enzyme, caspase 3, as well as by detection of changes in the expression of the proapoptotic and antiapoptotic proteins, BAX and Bcl-2.<sup>79</sup> Several IGF inhibitors are currently being tested in clinical trials in several tumor types, and we have initiated a phase II trial of an anti-IGFR monoclonal antibody (MK 0646, Merck) for the treatment of carcinoid and islet-cell tumors, which is currently enrolling patients.

## CONCLUSIONS

Well-differentiated NETs pose an important challenge because of tumor heterogeneity, varying degree of aggressiveness, and the lack of standard regimens and guidelines for treatment. These tumors are relatively resistant to chemotherapy, and show minimal responsiveness to conventional chemotherapy. Early, often-quoted literature might well overstate the degree to which chemotherapy regimens have demonstrated meaningful activity. An understanding of tumor signaling mechanisms has led to promising agents that could target clinically important pathways. These agents are now under investigation in patients with NETs.

A crucial challenge will be to elucidate the genetic alterations that influence clinical phenotype. Such information will improve our understanding of which patients will maintain their active quality of life with only minimal disease growth and which patients will, unfortunately, have a more aggressive course. Such genomic predictors have yet to be elucidated. In addition, clearly defined populations of patients and consistent assessment criteria are critical for future trials of this tumor type.

## KEY POINTS

- Patients with well-differentiated neuroendocrine tumors (NETs), the most common of which are carcinoid tumors and islet-cell carcinomas, typically present with metastatic disease
- Metastatic disease can be followed expectantly as it is often slow-growing and does not require intervention for many months to years
- Once the NET progresses or is symptomatic despite somatostatin-analog treatment, therapeutic options are extremely limited and no therapy is currently considered standard
- Tumor heterogeneity, the varying degree of aggressiveness, and the lack of standard regimens and guidelines for NET treatment pose a substantial clinical challenge
- Well-differentiated NETs exhibit diverse clinical outcomes, which can sometimes be stratified by certain histopathological features including cytological grade degree, angioinvasion, proliferative index (as assessed by mitotic index and Ki67), tumor size, presence of metastases, and functional activity
- An understanding of tumor signaling mechanisms has led to the development of promising agents that could target clinically important pathways, but an urgent need remains for genetic markers that identify the clinical phenotypes

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**Competing interests**

DL Reidy has declared an association with the following company: Merck. LB Saltz has declared associations with the following companies: Merck and Roche. See the article online for full details of the relationships. LH Tang has declared no competing interests.

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