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Systemic Therapy for the Management of Neuroendocrine Tumor Liver Metastases

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare, heterogeneous group of cancers with increasing incidence. As expected, the prognosis for patients with metastatic disease is worse than for those with localized disease. The use of systemic therapy is only indicated in patients with metastatic disease, and treatment options depend on tumor grade and site of the primary tumor. Somatostatin analogues are the mainstay of treatment in grade 1 and grade 2 intestinal neuroendocrine tumors, and their combination with targeted therapies, liver-directed therapies, and peptide receptor radionuclide therapy has resulted in extended overall survival. Treatment options for grade 1 and grade 2 pancreatic NETs include somatostatin analogues, liver-directed therapy, targeted therapies, cytotoxic chemotherapy and peptide receptor radionuclide therapy. Grade 3 neuroendocrine carcinomas are aggressive and associated with poor survival. While systemic chemotherapy is the mainstay of therapy for patients with this disease, the data for effective therapies in this disease are very limited, and clinical trials assessing chemotherapy regimens are ongoing.

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Epidemiology and Clinical Presentation

Gastroenteropancreatic neuroendocrine tumors are rare malignancies; however they have demonstrated increasing incidence over the last few decades. A retrospective study of the Surveillance, Epidemiology, and End Results (SEER) database reported that from 1973 to 2007, the incidence of GEP-NETs in the United States increased from 1.00 per 100,000 to 3.65 per 100,000 [1]. This phenomenon may be the result of increased awareness of the disease among physicians and improved diagnostic testing.

As diagnostic tools improve, it is increasingly evident that GEP-NETs represent a heterogeneous group of cancers, arising from neuroendocrine cells throughout the gastroenteropancreatic system and demonstrating a range of histopathologic features and clinical behavior. In an attempt to lessen ambiguity in defining neuroendocrine

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Table 22.1 2010 WHO classification scheme

WHO class	Definition	Ki-67 index (%)	Mitotic count (per 10 hpf[a])	Grade
1	NET[b]	≤2	<2	G1
2	NET	3–20	2–20	G2
3	NEC[c]	>20	>20	G3
4	MANEC[d]	N/A[e]	N/A	N/A
5	Hyperplasia/dysplasia	N/A	N/A	N/A

[a]*hpf* high-powered field
[b]*NET* neuroendocrine tumor
[c]*NEC* neuroendocrine carcinoma
[d]*MANEC* mixed adeno-neuroendocrine carcinoma
[e]*N/A* not applicable

neoplasms, the World Health Organization (WHO) published a classification scheme in 2010, stratifying GEP-NETs based on their proliferation rate (Table 22.1) [2].

In addition, GEP-NETs demonstrate a range of clinical manifestations. Functional tumors can produce symptoms related to hormone secretion, whereas nonfunctional tumors do not secrete hormones but can be symptomatic due to tumor bulk [3]. Functional tumors arising from the midgut (jejunum, ileum, appendix, proximal colon), also called carcinoids, may result in carcinoid syndrome. These patients have symptoms related to increased serotonin production including flushing and diarrhea [4]. Symptoms often develop after the tumor is metastatic, and patients with bulky liver disease have an increased risk of developing cardiac carcinoid, a rare syndrome characterized by the right-sided endocardial deposition of fibrous plaques [4]. A small proportion, approximately 10%, of pancreatic NETs are also functional and can produce a variety of symptoms based on the type of cell involved and hormone produced [5]. Such tumors may include gastrinomas, VIPomas (vasoactive intestinal peptide), glucagonomas, insulinomas, and somatostatinomas [3]. Treatment strategies for these tumors are directed toward symptom control as well as antiproliferation.

Among all types and grades of tumor, the presence of metastatic disease is common, particularly involving the liver. At diagnosis, an estimated 40–50% of tumors are already metastatic, likely due to the indolent behavior of many GEP-NETs [6, 7]. As would be expected, the presence of metastasis is a poor prognostic factor, with primary tumor site and tumor grade also carrying prognostic significance [8, 9]. In a retrospective SEER database study of 35,618 patients, those with metastatic disease had a markedly worse median overall survival (OS) as compared with those with localized disease. Patients with metastatic well-differentiated tumors had a significantly worse median OS of 33 months as compared to 223 months in patients with localized disease. Among patients with poorly differentiated tumors, median OS was 5 months in patients with metastatic disease as compared to 34 months in patients with localized disease [9]. In addition, pancreatic neuroendocrine tumors (PNETs) carry a worse prognosis than intestinal primary tumors, with a median OS of 24 months in metastatic PNETs and 56 months in those with metastases from a small bowel primary [9].

Given that patients with metastatic disease do not have a curable condition, there is ongoing investigation for effective treatment strategies. While curative surgery is available for resectable tumors and may at times be used in patients with metastatic disease to debulk tumor burden and/or provide palliative benefit, multimodality therapy for unresectable or metastatic tumors is aimed at controlling symptoms and prolonging life. Treatment modalities for each group of tumors are discussed in detail below. Table 22.2 summarizes the major phase II/III studies, and Table 22.3 summarizes ongoing clinical trials.

Table 22.2 Major randomized phase II/III trials in G1/G2 neuroendocrine tumors

	N	Tumor type	Primary endpoint	Treatment arms	Result	Statistical benefit
PROMID Rinke et al. 2009 [11]	85	Well-differentiated midgut NETs	TTP[a]	• Octreotide LAR • Placebo	• 14.3 mos[b] • 6 mos	HR[c] 0.34, $p = 0.000072$
RADIANT-2 Pavel et al. 2011 [17]	429	G1/G2 NETs	PFS[d]	• Everolimus + octreotide LAR • Octreotide LAR	• 16.4 mos • 11.3 mos	HR 0.77, $p = 0.026$
RADIANT-3 Yao et al. 2011 [30]	410	G1/G2 NETs	PFS	• Everolimus • Placebo	• 11 mos • 4.6 mos	HR 0.35, $p < 0.001$
Raymond et al. 2011 [33]	171	Well-differentiated PNETs	PFS	• Sunitinib • Placebo	• 11.4 mos • 5.5 mos	HR 0.42, $p < 0.001$
CLARINET Caplin et al. 2014 [13]	204	Well- or moderately differentiated nonfunctioning NETs	PFS	• Lanreotide • Placebo	• Not reached • 18 mos	HR 0.47, $p < 0.001$
RADIANT-4 Yao et al. 2016 [18]	302	Well-differentiated nonfunctional NETs	PFS	• Everolimus • Placebo	• 11 mos • 3.9 mos	HR 0.48, $p < 0.00001$
Wolin et al. 2015 [53]	110	Carcinoids	% pts with symptom control	• Pasireotide LAR • Octreotide LAR	• 20.9% • 26.7%	OR[e] 0.73, $p = 0.53$
CALGB 80701 Kulke et al. 2015 [36]	150	Well- or moderately differentiated PNETs	PFS	• Everolimus + bevacizumab • Everolimus	• 16.7 mos • 14.0 mos	HR 0.80, $p = 0.12$ ($\alpha = 0.15$)
NETTER-1 Strosberg et al. 2017 [28]	229	Well-differentiated midgut NETs	PFS	• ^{177}Lu-Dotatate + best supportive care • Octreotide	• Rate of PFS at 20 mos was 65.2% • 10.8%	HR 0.21, $p < 0.0001$
SWOG S0158 Yao et al.	427	G1/G2 NETs	PFS	• Octreotide + bevacizumab • Octreotide + interferon-alpha	• 16.6 mos • 15.4 mos	HR 0.93, $p = 0.55$

[a]*TTP* time to progression
[b]*mos* months
[c]*HR* hazard ratio
[d]*PFS* progression-free survival
[e]*OR* odds ratio

Table 22.3 Ongoing clinical trials

	Type of study	Estimated completion date	Estimated enrollment	Patient population	Treatment arms	Primary endpoint
NCT01841736 (A021202)	Phase II	Dec 2016	165	G1/G2 GI NETs	• Pazopanib • Placebo	PFS[a]
NCT01824875 (E2211)	Phase II	Jul 2017	145	Advanced PNETs	• Temozolomide • Temozolomide + capecitabine	PFS
NCT02820857	Phase II	Jan 2020	124	G3 NEC, 2nd line setting	• FOLFIRI + bevacizumab • FOLFIRI	OS[b]
NCT02113800	Phase II	Feb 2018	40	G3 NEC, 2nd line setting	• Everolimus	AE[c]
NCT02595424 (EA2142)	Phase II	Jan 2018	126	G3 NEC, 1st line setting	• Temozolomide + capecitabine • Cisplatin + etoposide	PFS

[a]*PFS* progression-free survival
[b]*OS* overall survival
[c]*AE* adverse effects

Grade 1 and 2 Gastrointestinal Neuroendocrine Tumors

Somatostatin Analogues

Grade 1 and grade 2 gastrointestinal neuroendocrine tumors, also called carcinoids, are slow-growing cancers generally unresponsive to cytotoxic chemotherapy, and the mainstay of treatment is somatostatin receptor inhibition. Given their high levels of expression on intestinal NETs, somatostatin receptors are a natural target for somatostatin analogues and provide benefit in the form of both symptom relief for functional tumors and antiproliferative benefit [10]. The binding of somatostatin to its receptors on the tumor surface results in the inhibition of serotonin production by the tumor. While the body does produce somatostatin, the therapeutic use of endogenous somatostatin is limited by its half-life, as it is rapidly inactivated [10]. Octreotide was the first synthetic somatostatin analogue and was eventually developed into a long-acting repeatable (LAR) octreotide acetate. Octreotide and other somatostatin analogues are effective in controlling hormone secretion from functional NETs and thus were initially approved for symptomatic management of carcinoid syndrome.

In addition to symptom control, octreotide has an antitumor effect in well-differentiated midgut carcinoids. The PROMID phase III trial randomized 85 patients with treatment-naïve well-differentiated metastatic midgut NETs to receive either octreotide LAR or placebo [11]. This approach demonstrated a benefit in median progression-free survival (PFS) of 14 months in the octreotide group versus 6 months in the placebo group (HR 0.34, 95% CI 0.20–0.59, $p = 0.000072$). A subgroup analysis suggested no difference in time to progression between patients with a functional and a nonfunctional tumor (HR 1.38, 95% CI 0.81–2.37, $p = 0.24$). This study overall reported an antitumor benefit for octreotide in both functional and nonfunctional well-differentiated metastatic midgut NETs, and as a result, it is the current frontline standard of care therapy for treatment of this disease [12].

To further evaluate the antiproliferative benefit of somatostatin analogues in a broader group of well-differentiated NETs, lanreotide was tested in patients with nonfunctional tumors in the phase III CLARINET trial [13]. A total of 204 patients with an advanced grade 1 or 2 NET of the pancreas, midgut, hindgut, or unknown origin were randomized to receive lanreotide or placebo. A clear benefit in median PFS was shown in the lanreotide group (median PFS not reached) versus 18 months in the placebo group. Eighty-eight patients continued on an open-label extension study and ultimately showed a median

PFS in the lanreotide group of 32.8 months [14]. Of note, this study included more patients with a large hepatic tumor volume compared with the PROMID study. Positive results from this study confirmed that treatment with a somatostatin analogue could be initiated as treatment for patients with well-differentiated NETs arising in a primary site beyond just the midgut and also in patients with either a functional or nonfunctional tumor. Patients harboring a large tumor volume in the liver also derived survival benefit.

Targeted Therapies

The mammalian target of rapamycin (mTOR) pathway has been implicated in neuroendocrine tumor pathogenesis [15]. As such, everolimus, an oral inhibitor of mTOR, has been studied extensively as a treatment option in G1 and G2 NETs. An initial phase II study combining everolimus and octreotide showed a modest response rate of 20% in 60 patients with carcinoid and PNETS [16]. The combination was further evaluated in RADIANT-2, a phase III trial that randomized 429 patients with previously treated advanced carcinoid to everolimus plus octreotide or placebo plus octreotide [17]. The median PFS for the everolimus group compared with the placebo group was 16.4 months versus 11.3 months; however this did not achieve statistical significance (HR 0.77, 95% CI 0.59–1.00, $p = 0.026$). RADIANT-4 was subsequently designed to test everolimus as a monotherapy in patients specifically with nonfunctioning tumors. A total of 302 patients with previously treated G1 and G2 nonfunctional NETs of intestinal and lung origin were randomized to everolimus or placebo [18]. Median PFS was 11 months in the everolimus group compared with 3.9 months in the placebo group (HR 0.48, 95% CI 0.35–0.67, $p < 0.00001$), confirming a role for everolimus in nonfunctioning low- to intermediate-grade NETs of the lung and GI tract.

Interferon-Alpha

Interferon (IFN) was first studied as a therapeutic strategy in neuroendocrine tumors in the 1980s, when it was becoming clear that cytotoxic agents were largely ineffective. Interferon-alpha was felt to be a promising antiproliferative agent, but its use was limited by its toxicity. A phase II trial enrolling patients with progressive well-differentiated GI and pancreatic NETs showed that pegylated-interferon-alpha (PEG-IFN) produced a partial response or stable disease in 13 of 17 patients, with no grade 3 or 4 toxicities [19]. Interest in combining interferon with octreotide and comparing it to new anti-angiogenic targeted agents led to the SWOG 0158 study. In this phase III trial, 427 patients with an advanced G1 or G2 NET were randomized to octreotide plus IFN versus octreotide plus bevacizumab. Although there was a higher radiographic response rate in the bevacizumab group compared with the interferon-alpha group (12% versus 4%), there was no PFS difference between the two treatment arms (HR 0.93, 95% CI 0.73–1.18, $p = 0.55$). While one arm did not appear superior to the other, given that interferon-alpha and octreotide both have activity in this disease entity, this study suggested that bevacizumab and interferon-alpha likely have similar antitumor activity [20].

Peptide Receptor Radionuclide Therapy (PRRT)

With the many attractive features of somatostatin analogues—an effective antiproliferative agent, an effective therapy for reducing hormone-mediated symptoms, a tumor-specific targeted therapy, and the ability to use radiolabeled somatostatin analogues to visualize NETs radiographically—peptide receptor radionuclide therapy (PRRT) was developed as a treatment strategy in carcinoids. PRRT was initially studied using [^{111}In-DTPA^{0}]octreotide, the radiolabeled somatostatin analogue used for the octreotide scan. Unfortunately, tumor responses with this agent were uncommon [21]. However, interest in this modality continued as more radiolabeled somatostatin analogues were developed. [^{90}Y-DOTA^{0},Tyr^{3}]octreotide showed promise in inducing partial and complete remissions

[22–24], and the newest radiolabeled somatostatin analogue, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, showed similar activity but less hematologic toxicity than [^{90}Y-DOTA^{0},Tyr^{3}]octreotide in a phase I/II trial comparing the two [25–27]. PRRT utilizing [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, or ^{177}Lu-Dotatate, ultimately showed a progression-free survival benefit over octreotide in the phase III NETTER-1 study [28]. In this trial, 229 patients with well-differentiated (Ki-67 < 20%) metastatic midgut NETs, with the presence of somatostatin receptors confirmed by octreotide scan and progression on previous octreotide LAR, were randomized to ^{177}Lu-Dotatate plus octreotide LAR 30 mg versus high-dose octreotide LAR 60 mg alone. At the time of initial analysis, the 20-month progression-free survival rate was 65.2% in the ^{177}Lu-Dotatate group (95% CI 50.0–76.8) versus 10.8% in the control group (95% CI 3.5–23.0), with the median PFS not yet reached in the ^{177}Lu-Dotatate group and 8.4 months in the control group (HR 0.21; 95% CI 0.13–0.33, $p < 0.0001$). The response rate, a secondary objective, was 18% in the PRRT group vs 3% in the octreotide alone group ($p < 0.001$). The most common adverse effects in the PRRT group were nausea (59%) and vomiting (47%), compared with the control group (12% and 10%, respectively). Grade 3 or 4 toxicities were uncommon in the PRRT group, including lymphopenia (9%), vomiting (7%), diarrhea (3%), fatigue (2%), and thrombocytopenia (2%), compared with no grade 3 or 4 hematologic toxicities in the control group. These results demonstrate that PRRT is strikingly efficacious in terms of its progression-free survival benefit without significant added toxicities as compared with previous therapies making it an exciting new treatment modality for the management of metastatic carcinoid. A great unknown at this time, however, is where this modality should be used in relation to other treatment options. This is of significant importance as there is some overlap in toxicity profiles, and it would be ideal to minimize toxicities experienced so as to allow patients to ultimately receive all forms of available treatment.

G1/G2 Pancreatic Neuroendocrine Tumors

Somatostatin Analogues

While somatostatin analogues are used for symptom control for carcinoids and functional G1 and G2 pancreatic neuroendocrine tumors (PNETs), the data is less clear on an antiproliferative tumor benefit in nonfunctional PNETs. While the PROMID study excluded PNETs, the phase III CLARINET study included 91 well- and moderately differentiated PNETs with a Ki-67 < 10% (out of a total $n = 204$). The progression-free survival in the overall study population of patients lanreotide as part of the open-label extension study was reported as 32.8 months [14], versus a median PFS of 18 months in the placebo arm from the core study [13]. As such, there is consensus that somatostatin analogues may be used as an antiproliferative agent in the management of PNETs, particularly in patients with a Ki-67 < 10%. Despite the Ki-67 cutoff identified in this study, this is generally not used to make treatment decisions for patients receiving PNETs, and a large majority of patients with a well- or moderately differentiated PNET will receive treatment with a somatostatin analogue. Further studies delineating a Ki-67 cutoff value are needed in order to stratify patients to receive somatostatin analogues versus initiation of more aggressive therapy [6].

Targeted Therapies

Prior to the advent of targeted therapies, cytotoxic chemotherapy was the only approved treatment option in this disease. The activity of everolimus in intestinal NETs as discussed previously prompted evaluation in advanced PNETs. A single-arm phase II study assessing daily everolimus in patients with PNETs who had developed disease progression while on cytotoxic therapy demonstrated a median PFS of 16 months [29]. The activity of everolimus was subsequently confirmed by comparing it to placebo in the phase III RADIANT-3 study, which randomized

410 patients with advanced G1 and G2 PNETs to receive either everolimus or placebo. Median PFS was 11 months in the everolimus group versus 4.6 months in the placebo group, establishing everolimus as a therapeutic standard for patients with advanced PNETs [30].

In addition to mTOR inhibitors, inhibition of angiogenesis has been investigated in G1 and G2 PNETs, which are highly vascular tumors and are known to express vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptors (PDGFR) [31]. Sunitinib, a small molecule tyrosine kinase inhibitor with activity against VEGFR, PDGFR, as well as other growth factor receptors, was evaluated in a phase II study, demonstrating a response rate of 16.7% and maintaining stable disease in 68% of patients with PNETs ($n = 66$) [32]. Of note, there did not appear to be activity in carcinoids, with a response rate of only 2.4% in 41 carcinoid patients. A phase III study confirmed the efficacy of sunitinib in PNETs, randomizing 171 patients to receive either sunitinib or placebo [33]. The study was stopped early in favor of the sunitinib group, with a median PFS of 11.4 months compared to 5.5 months in the placebo group, establishing sunitinib as a treatment standard in PNET. Based on the success of sunitinib, another VEGF inhibitor, bevacizumab, was found in a single-arm phase II study to have a median PFS of 13.6 months in 22 patients with G1/G2 advanced PNETs [34], similar to the progression-free survival from the phase III sunitinib study.

As both mTOR and angiogenesis pathways had been implicated in the pathogenesis of this disease and agents targeting both of these pathways had shown treatment benefit, dual pathway inhibition has been investigated. Bevacizumab was studied in combination with temsirolimus in a single-arm, phase II study, showing a response rate of 41% and a median PFS of 13.2 months in 58 patients with advanced G1/G2 PNETs [35]. In PNETs, combination therapy with bevacizumab and everolimus was studied in CALGB 80701, a phase II trial that randomized 150 patients with advanced PNETs to everolimus plus bevacizumab or everolimus alone [36]. The authors demonstrated an improved progression-free survival in the combination arm as compared to everolimus alone with a PFS of 16.7 months versus 14 months, respectively ($\alpha = 0.15$; HR 0.80, 95% CI 0.55–1.17, $p = 0.12$). Also observed was an increased response rate in the combination arm, as compared to single-agent everolimus at 31% and 12%, respectively ($p = 0.005$). Despite these positive results, the overall rate of grade 3 or 4 adverse events was much higher in the combination arm compared with everolimus alone at 81% vs 49%. This degree of toxicity, along with a modest PFS benefit, is likely to limit the use of combination therapy with an mTOR inhibitor and an anti-angiogenic agent in clinical practice. However, aside from cytotoxic chemotherapy, this regimen does show one of the better response rates so may be used in particular cases where a reduction in tumor burden is desired.

Additional tyrosine kinase inhibitors have also been investigated in early clinical trials. In a phase II study of advanced PNETs and carcinoids, sorafenib, a multi-targeted kinase inhibitor, demonstrated a modest response rate of 10% [37]. A phase II study of pazopanib, a multitargeted agent against VEGF, PDGFR, and c-KIT, in 52 patients with advanced G1 and G2 NETs showed a 21.9% response rate in PNETs ($n = 32$); however no response was detected in the carcinoid group ($n = 20$) [38]. Median PFS, a secondary endpoint, was promising in both groups, 14.4 months in the PNET cohort (95% CI 5.9–22.9) and 12.2 months in the carcinoid cohort (95% CI 3–19.9). Finally, cabozantinib, a multitargeted kinase inhibitor against VEGF, MET, AXL, and RET, has been studied in a single-arm phase II trial that enrolled 61 patients with advanced PNETs ($n = 20$) and carcinoids ($n = 41$) [39]. Response rate, the primary endpoint, was found to be 15% in the PNET cohort (95% CI 5–36) and 15% in the carcinoid cohort (95% CI 7–28). Median PFS, a secondary endpoint, was 21.8 months in the PNET cohort (95% CI 8.5–32) and 31.4 months in the carcinoid cohort (95% CI 8.5-not reached), suggesting an improvement in survival with cabozantinib compared with historical results. A randomized phase III study assessing pazopanib versus placebo in patients with advanced carcinoid has been conducted with

results pending at this time (A021202, NCT01841736). A phase III study assessing cabozantinib in PNETs and carcinoids is currently in development.

Cytotoxic Chemotherapy

The main goal of cytotoxic therapy in PNETs is to reduce the tumor burden in bulky or progressive disease. This can be beneficial in regard to controlling tumor growth as well as decreasing the level of hormone production in patients with functional tumors. As such, response rate is an important endpoint in these clinical trials. Initially, streptozocin combinations were assessed for tumor response in PNETs. Moertel et al. randomized 105 patients with advanced PNETs to streptozocin plus 5FU versus streptozocin plus doxorubicin versus chlorozotocin alone [40]. The combination of streptozocin plus doxorubicin offered a PFS benefit of 20 months as compared with 6.9 months in the streptozocin plus 5FU group. In another single-arm phase II study, the triplet regimen of streptozocin, doxorubicin, and 5FU produced a response rate of 30% in 84 patients with advanced PNETs and a median PFS of 9.3 months [41]. Despite the favorable results observed in these studies, streptozocin-based regimens are not commonly used in clinical practice due to the unfavorable side effect profile including nausea, vomiting, myelosuppression, renal insufficiency, and fatigue.

Temozolomide-based regimens have demonstrated promising results in several early clinical studies. A combination of temozolomide and thalidomide was evaluated in a single-arm phase II study of 29 patients with advanced NETs. In this study, a response rate of 45% was observed in PNETs ($n = 11$), whereas 7% of carcinoid patients showed tumor response ($n = 14$) [42]. Temozolomide in combination with bevacizumab also showed promise in a single-arm phase II study of 33 patients with advanced NETs, with a response rate of 33% in PNETs ($n = 15$) and 0 carcinoid patients showing a response [43]. The combination of temozolomide and capecitabine was studied in a single-center retrospective study of 30 patients with PNETs. In this study a response rate of 70% was reported [44]. As this was the highest response rate observed among any treatment regimen for treatment of this disease, a large prospective study was conducted assessing temozolomide vs temozolomide plus capecitabine in patients with advanced PNETs (E2211). The results of this important trial are pending at this time.

G3 Neuroendocrine Carcinomas

Cytotoxic Chemotherapy

G3 neuroendocrine carcinomas (NECs) are aggressive cancers, and treatment is limited to cytotoxic chemotherapy. There is little data to guide therapy; however much of the guidelines for high-grade neuroendocrine carcinomas are extrapolated from clinical trials in small cell carcinoma [45, 46]. Furthermore, most of the data evaluating a NEC-specific population are retrospective or small phase II studies. In 1999, a retrospective study examined the response rates of 53 patients with well-differentiated NETs or poorly differentiated NECs after receiving cisplatin plus etoposide chemotherapy [47]. The poorly differentiated group had a much higher response rate of 41% as compared with 9% in the well-differentiated group. The three-drug combination of carboplatin, etoposide, and paclitaxel was evaluated in a phase II study of 78 patients with poorly differentiated NECs. The reported response rate in this study was 53%, with no obvious advantage in efficacy over standard doublet therapy [48]. As such, this three-drug combination is not commonly used; however taxane-based therapy is a common choice for second-line therapy.

Regimens other than platinum and etoposide have been investigated in small retrospective studies in the second-line setting. FOLFOX showed a partial response of 29% in a French single-center retrospective study of 20 patients [49]. Temozolomide, alone or in combination with capecitabine and with or without bevacizumab, showed a partial response of 33% in a retrospec-

tive study of 25 patients from two oncology centers in Norway and Sweden [50]. Based on the results of this study, a temozolomide-based regimen has been thought by many to be a potential alternative treatment strategy to platinum and etoposide chemotherapy. The efficacy of these regimens needs further evaluation; however prospective studies have historically been difficult due to the rarity of this disease. As platinum and etoposide have not ever been officially evaluated in G3 NECs previously, there is an ongoing randomized phase II clinical trial of cisplatin or carboplatin and etoposide versus temozolomide and capecitabine (EA2142, NCT02595424). The results of this study should finally provide some prospective data regarding the role of each of these treatment regimens in patients with advanced G3 NECs.

Whether this group of heterogeneous cancers can be further stratified is an ongoing question in G3 NEC. The NORDIC study in 2012 analyzed clinical data from 74 studies in G3 NEC for predictive and prognostic factors [51]. This study identified a possible subgroup of patients with an improved survival. Patients with a Ki-67 less than 55% had a median survival of 14 months compared with 10 months in patients with Ki-67 greater than 55%. The data also suggested that patients with a Ki-67 less than 55% are not as responsive to platinum-based chemotherapy compared to patients with a Ki-67 greater than 55% (RR 15% versus 42%). These results underscored the idea that NECs are a heterogeneous group of cancers that are not fully classified and with a wide range of clinical behavior and prognosis [52]. Further delineating tumor types in this group and offering treatment that best fits their clinical risk would greatly benefit this patient population, and this is an area of active investigation.

Conclusion

GEP-NETs are a diverse group of cancers, and systemic therapy for metastatic disease is an ongoing area of clinical investigation. In particular, PRRT in well-differentiated carcinoids and PNETs has made a dramatic improvement in extending progression-free and overall survival. Targeted small molecule therapies in combination with somatostatin analogues have proved to be effective in G1/G2 intestinal and pancreatic NETs. With the rapid evolution of treatment options for patients with both PNETs and carcinoids, one unknown question at this time is how to best sequence these agents so as to provide patients with the greatest longevity while keeping toxicity to a minimum. As patients with these diseases have relatively long periods of survival, this question will likely take many years to answer, but it is an active area of investigation. G3 NECs continue to be associated with poor survival and limited treatment options, and ongoing clinical trials may help to further risk stratify this group.

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