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Update on management of midgut neuroendocrine tumors

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Abstract

Midgut neuroendocrine tumors are typically indolent but can be fatal when advanced. They can also cause significant morbidity due to the characteristic carcinoid syndrome. Somatostatin analogs continue to be the mainstay of treatment given their antiproliferative properties, as well as inhibitory effects on hormones that cause carcinoid syndrome. There have been several recent advances in the systemic therapy of these tumors including consolidation of somatostatin analogs as the cornerstone of therapy, completion of pivotal trials with mTOR inhibitors, and the establishment of novel approaches including peptide receptor radionuclide therapy and oral inhibitors of peripheral tryptophan hydroxylase in tumor and symptom control, respectively. In this review article, the recent advances are summarized and an updated approach to management is proposed.

Keywords

carcinoid; everolimus; lanreotide; neuroendocrine; peptide receptor radionuclide therapy; octreotide; telotristat

Background

Neuroendocrine tumors (NETs) are rare tumors that originate primarily from the neuroendocrine cells of the diffuse endocrine system. The term ‘carcinoid’ tumor is used to refer to extra-pancreatic NETs underscoring the distinct biology and clinical behavior of pancreatic neuroendocrine tumors. Neuroendocrine tumors maybe subdivided based on their embryonic sites of origins into foregut, midgut and hindgut NETs. The embryonic midgut includes the distal part of duodenum, jejunum, ileum, ascending colon, appendix and proximal two-thirds of transverse colon. Small intestine is the most common site for NETs in the GI tract [1,2], where most NETs originate within 60 cm of ileocecal valve [3]. According to the most recent analysis of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the overall incidence rate of gastrointestinal neuroendocrine tumors (GI-NETs) has increased almost fivefold between

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1975 and 2004. This is evident for almost all gastrointestinal organ sites, particularly for midgut neuroendocrine tumors (MNETs). Although the exact reasons for this dramatic increase are unclear, they could be attributed to the higher rates of detection with advances in endoscopic and radiologic imaging techniques, as well as better pathological classification of exocrine and endocrine tumors [2,4].

Clinical presentation & classification

MNETs may be asymptomatic at the time of presentation when they are usually found incidentally during surgery (e.g., appendectomy) or work up for other reasons [5]. When symptomatic, the signs and symptoms usually occur as a result of either mechanical complications (such as bleeding, obstruction), or due to release of bioactive substances into the bloodstream [6]. These vasoactive peptides (e.g., serotonin, histamine, tachykinin, prostaglandin, etc.) produce a constellation of signs and symptoms in the skin, GI tract and heart, which is called carcinoid syndrome. The manifestations are diverse and may include diarrhea, flushing, abdominal cramping, telangiectasia's, bronchospasm (wheezing), valvular lesions (aka carcinoid heart) and rarely pellagra due to chronic and severe deficiency of niacin [7]. The liver usually inactivates these peptides and hormones, therefore carcinoid syndrome in MNETs usually happens only after the development of hepatic metastases. Of note, 71% of MNETs are metastatic at the time of presentation [8], and the liver is the primary site of metastasis. Classic carcinoid syndrome has been reported to occur in approximately 8–28% of patients with neuroendocrine tumors, most commonly with MNETs [9,10]. NETs including MNETs maybe classified into well differentiated (further subclassified into low and intermediate grade) and poorly differentiated (high grade) based on proliferative indices such as Ki-67 and/or mitotic index (Table 1). In 2006 and 2007, the European Neuroendocrine Tumor Society (ENETS) suggested a new staging classification accompanied with a grading system [11]. This system was adopted by American Joint Committee on Cancer (AJCC), and was also endorsed by WHO in 2010 (Tables 2 & 3) [12,13].

Management

Multiple guidelines are currently available for the management of MNETs including those from the National Comprehensive Cancer Network (NCCN), the European Neuroendocrine Tumor Society (ENETS) and The North American Neuroendocrine Tumor Society (NANETS) [5,6,14]. Although there are some variations between these different guidelines, in general, management of MNET is based on multiple factors including stage, grade, extent of disease, presence of symptoms, performance status and organ function. It is important to note that the best choice of treatment for a patient should be determined in a multidisciplinary fashion while incorporating patients' preferences. In fact, for some patients with no symptoms, low tumor burden and stable disease based on markers and scans, observation may be appropriate; for instance, evidence for this approach is provided by the recent Phase III CLARINET trial in which the median progression-free survival (PFS) of the placebo arm was 18 months (95% CI: 12.1–24 months) [15].

• Surgery

Surgery is considered the only curative measure and should be offered to patients with resectable tumors regardless of presence of liver metastases although recurrence rates after resection of metastatic disease are typically very high. Currently, there are no data supporting the use of adjuvant therapy after complete resection [6]. Surgery may also be considered in MNETs to alleviate local symptoms such as bowel obstruction from the primary tumor or to prevent future complications such as bowel obstruction and/or mesenteric vascular compromise from regional lymphadenopathy. For asymptomatic primary MNETs with unresectable metastases, the role of surgery is not clearly defined. Some studies (including UKINETS study), suggest that resection of asymptomatic primary tumor in this setting may improve survival [16,17]; while others such as study performed by Strosberg *et al.* did not find survival benefit with resection of primary tumor in metastatic MNETs [18]. Therefore, resection of primary tumor in metastatic MNETs is unclear and is not routinely performed at most centers. Another aspect of debate is the role of debulking with an intent to remove at least 90% of metastatic disease in patients with liver predominant disease. While some studies suggest survival benefit with this approach others have shown contradictory findings [19,20]. The indolent nature of the disease and the inherent biases involved in retrospective studies has limited our ability to assess the true impact of this approach. Currently, debulking surgery continues to be a recommendation in major consensus guidelines including those from the NCCN if near-complete resection of tumors can be achieved. Liver-directed therapy (including liver resection, arterial embolization, chemoembolization or radioembolization) should be considered for unresectable tumors, which are mainly confined to the liver. Data to support the sequence of regional versus systemic therapy are insufficient. The first-line systemic treatment for unresectable and/or metastatic MNETs is typically somatostatin analogs [14].

• Somatostatin analogs

Somatostatin (SST) is a native cyclic polypeptide comprising either 14 or 28 amino acids which was first isolated and described as a 'growth hormone inhibitor' in 1973 [21]. It is widely distributed throughout the body and works via activation of one or more of the five different G-protein-coupled somatostatin receptor subtypes ($sstr_{1-5}$) with differential effects [22], but all eventually leading to physiological inhibition of multiple functions including decrease in secretion of various exocrine and endocrine hormones [21,23]. It was demonstrated that tumors originating from neuroendocrine cells express these receptors in a very high density (with well-differentiated NETs usually expressing in much higher levels compared with poorly differentiated neuroendocrine carcinomas), and this observation has led to the development of diagnostic and therapeutic options. SST has multiple cleavage sites and is degraded quickly in the bloodstream (half-life about 2–3 min), severely limiting its clinical use. By shortening the length along with other modifications of the SST polypeptide chain, longer lasting somatostatin analogs (SSAs) have been developed (e.g., octreotide, lanreotide [LAN] and pasireotide) [24]. Radionuclide scintigraphy using a radiolabeled SSA, indium-111 pentetreotide (octreoscan) is used to select patients for peptide receptor radionuclide therapy (PRRT) [25–27]. Among different subtypes of somatostatin receptors, $sstr_2$ is the most frequent subtype expressed in neuroendocrine tumors, followed by $sstr_1$ and $sstr_5$. Antisecretory effect of somatostatin and SSAs is mainly

mediated via activation of sstr_2 and sstr_5 . In addition, it has been established that activation of $\text{sstr}_{1, 2, 4, 5}$ results in G_1 cell cycle arrest and activation of sstr_2 and sstr_3 will lead to induction of apoptosis in tumor cells [28–30]. SSAs also exert indirect antiproliferative effects via inhibition of growth factor, hormone synthesis and angiogenesis which does not require the presence of somatostatin receptors [28]. Despite the antiproliferative properties of SSAs, for the first few decades the main application of these agents in NETs was to control the symptoms of carcinoid syndrome [31] and their use as antineoplastic agents was not established until much later [32].

Octreotide—Octreotide is an eight-residue SSA developed in the 1980s with high affinity to sstr_2 and sstr_5 . This agent was originally available in only in the subcutaneous form (sc.) with a half-life of 2 h. It was initially US FDA approved for symptom control of carcinoid syndrome and the profuse watery diarrhea associated with vasoactive intestinal polypeptide secreting tumors [33,34]. For convenience and improved compliance, the long-acting release (LAR) formulation was introduced in 1999. The typical starting dose for octreotide-LAR is usually 30 mg and can be administered every 4 weeks with intramuscular injection. This formulation is released slowly from microsphere and provides efficacy and safety results comparable to those with subcutaneous octreotide. It should be noted that it usually takes 2 weeks for this formulation to reach steady state. Therefore, coverage with short-acting agent during this time maybe required for symptom control [35]. The PROMID trial, a double-blind prospective randomized study evaluating 85 patients with advanced MNETs, showed that administration of octreotide LAR 30 mg im. monthly significantly increases time-to-progression (TTP) in comparison to placebo (14.3 vs 6 months, respectively, hazard ratio [HR]: 0.34; 95% CI: 0.20–0.59; $p = 0.000072$). Based on a small, unplanned subgroup analysis of this study, it was proposed that SSA is most beneficial in patients with low tumor burden in the liver, which was not substantiated in the later, larger CLARINET trial as discussed below [36]. Both in the initial publication and a later report of PROMID, there was a trend toward improvement in survival in the octreotide arm that was not significant perhaps related to significant cross over from the placebo arm at progression [37]. A recent analysis of the SEER-Medicare database evaluating 326 patients older than 65 years, in fact suggested that octreotide-LAR may provide a survival benefit for patients with distant stage disease [38]. Several retrospective studies have established the safety and potential efficacy of above-label doses of octreotide LAR (>30 mg im. every 4 weeks) for patients with refractory carcinoid syndrome. However, whether increased doses of octreotide are more effective in tumor control remains unanswered given that these studies are retrospective with significant variation in method, dosage (i.e., dose and frequency), patient populations and measurement of endpoints [39–45].

LAN—LAN is a cyclic heptapeptide SSA with similar binding profile to octreotide and has two available forms: sustained-release formulation administered intramuscularly every 2 weeks and extended-release which is injected subcutaneously every 4 weeks (Autogel aka depot form in the USA). LAN was demonstrated to be well tolerated and be as effective in reducing biochemical markers and symptoms especially in patients who are naive to SSA therapy [46–48]. It was also shown to result in stabilization of disease in small studies [49]. A more recent large, randomized, double-blind, Phase III study (CLARINET trial) compared

LAN 120 mg subcutaneous every 4 weeks (depot form) with placebo in 204 patients with grade 1 or 2 (Ki-67 <10%), non-functioning gastrointestinal NETs. The study demonstrated a significant improvement in the primary end point of progression-free survival, PFS with LAN (18 months vs not reached; HR: 0.47; 95% CI: 0.30–0.73) that was seen irrespective of the degree of tumor burden in the liver. Based on these results, LAN was approved by the FDA for the treatment of patients with unresectable, well-differentiated advanced gastroenteropancreatic neuroendocrine tumors (GEP-NET) [15]. In the CLARINET extension study, patients who had received LAN in CLARINET core study and had stable disease (n = 41) and patients who had received placebo in the core study (regardless of having progressive disease, n = 47) entered the single-arm open-label extension and received LAN 120 mg subcutaneous every 4 weeks and PFS as well as safety profile of LAN were evaluated. In the LAN-LAN group, median PFS was 32.8 months (95% CI: 30.9–68.0). In the placebo-LAN group, median time from first PD to subsequent PD or death was 14.0 months (95% CI: 10.1 to not calculable). Out of the 15 patients on placebo in the core study who did not have PD, only three have experienced PD in the extension study. The results of this study confirm long-term antitumor activity and survival benefits of LAN in GEP-NETs with progressive disease and demonstrates a consistent long-term safety profile and tolerability of this agent [50]. One subset analysis from CLARINET study in patients with MNET revealed consistent results with favorable safety profile in this subgroup with no adverse event related to the medication. Median PFS was not achieved in LAN group (which was 21 months in placebo) [51].

Pasireotide—Pasireotide is another SSA with a broader binding profile than octreotide and LAN (sstr_{1,2,3,5}) [52]. Given greater receptor binding affinity, pasireotide was suggested for continued symptomatic control in patients who have developed resistance or decreased response to other SSAs [53,54]. Pasireotide-LAR is the long-acting release form, which is usually administered 60 mg subcutaneous every 28 days. In an initial Phase II clinical trial, Kvols *et al.* investigated pasireotide in patients whose symptoms were inadequately controlled with octreotide-LAR, and also illustrated controlled diarrhea and flushing in 27% of cases and stable disease in more than half of the patients [55]. In contrast, a Phase III clinical trial comparing pasireotide-LAR versus octreotide-LAR (at 40 mg every 4 weeks) in 110 patients with metastatic GI-NETs whose symptoms were refractory to first-generation SSA, demonstrated no difference in the primary end point of symptom control between the two arms at 6 months. However, pasireotide-LAR showed significantly longer median PFS in comparison to octreotide-LAR (11.8 vs 6.8 months, HR: 0.46, p = 0.045) in a predefined exploratory analysis. The most common drug-related adverse effects were hyperglycemia (28.3%), fatigue (11.3%) and nausea (9.4%) [44]. Although severe toxicity with pasireotide is rare, the high rate of hyperglycemia may pose a concern for further development of pasireotide as a first-line agent in NETs [56].

Tachyphylaxis—In patients receiving SSAs for over 6–12 months, resistance or decreased response to therapy (referred as ‘escape from response’ or tachyphylaxis) has been reported. The proposed pathophysiological mechanisms for this poorly understood phenomenon include downregulation, internalization or even mutation of somatostatin receptors [57]. In this case, some experts advocate increasing the dose of SSA or

administration of ‘rescue’ doses of short-acting octreotide to relieve breakthrough symptoms [58].

Somatostatin analogs side effects—SSAs are usually very well tolerated with mild side effects. Local pain and erythema at the injection site may be noted. Systemic symptoms include mild nausea, abdominal discomfort, pancreatic insufficiency manifesting as mild hyperglycemia, bloating and loose stools due to malabsorption that can be alleviated with pancreatic enzyme supplements. These side effects are usually mild, dose dependent and resolve in the first few weeks of treatment [59,60]. Sludge formation and cholelithiasis can occur in up to 25–50% of patients due to reduction of postprandial gallbladder contractility. Despite high incidence of cholelithiasis, only 1% of patients with acute symptoms will need acute cholecystectomy [60]. According to NCCN guidelines, prophylactic cholecystectomy is recommended when performing surgery for patients with advanced NETs, given the risk of development of biliary symptoms and cholecystitis [14].

Carcinoid crisis

‘Carcinoid crisis’ refers to the hemodynamic compromise as a result of release of overwhelming amounts of serotonin and other vasoactive peptides into systemic circulation manifesting as flushing, hypo- or hyper-tension, diarrhea, severe bronchospasm and cardiac arrhythmia typically triggered by tumor manipulation or general anesthesia in patients with functional tumors [61]. Therefore, SSA should be available during surgical procedures in MNETs. The NCCN guidelines recommend administration of octreotide prior to induction of anesthesia in these patients [14]. A recent retrospective study performed by Massimino *et al.* on 97 patients of whom 90% received prophylactic and 56% received intraoperative dose of SSA revealed that 24% of patients experienced carcinoid crisis, regardless of presence of carcinoid syndrome and despite having received prophylactic octreotide. In this study, intraoperative complications occurred in both functioning (21%) and nonfunctioning (28%) tumors and presence of liver metastasis was the only true predictive factor for development of carcinoid crisis [62]. Further studies are required to clarify the indications and outcomes associated with prophylactic SSA in preoperative setting. Until then, all patients with carcinoid syndrome and elevated urinary 5-HIAA must be considered for prophylactic SSA and should be closely monitored for carcinoid crisis during invasive procedures.

Interferon

Interferon (IFN) has been extensively investigated in the treatment of neuroendocrine tumors since the 1980s and was shown to inhibit tumor growth [63] by different mechanisms including delaying progression through S phase into G2/M, inhibition of angiogenesis and immunomodulation via upregulating of major histocompatibility class I antigens [63–65]. In initial studies, IFN- α was shown to improve clinical symptoms in refractory carcinoid syndrome and decrease tumor markers in 50% of patients [66]. In 2003, Kölby *et al.* reported that addition of IFN- α to octreotide is superior to monotherapy with octreotide in therapy of midgut neuroendocrine tumors [67]. Other studies have suggested comparable antiproliferative effects of IFN- α to SSA [49,68]. In conclusion, although IFN continues to be part of multiple consensus guidelines for treatment of progressive MNET and refractory

carcinoid syndrome, widespread use has been limited by its safety profile and side effects including fatigue, depression, myelosuppression, malaise and weight loss.

VE GF inhibitors

Neuroendocrine tumor, including well-differentiated MNET are hypervascular tumors that show strong VEGF expression [69]. Higher expression of VEGF in these tumors is associated with metastasis and poorer outcome [70].

• Bevacizumab

Combination of bevacizumab (BEV) with multiple agents has been studied in prior clinical trials [71–73]. BEV with temozolomide in 34 patients (including 56% with carcinoids and 44% with pancreatic neuroendocrine tumors [pNETs]) revealed a median PFS of 11 months (14.3 months for pNETs vs 7.3 months for carcinoid tumors) [71]. Another trial evaluating BEV versus pegylated IFN- α -2b in combination with octreotide suggested superior antitumor activity of BEV over pegylated IFN- α -2b with 18 week PFS of 95 vs 68% [73]. The result of BETTER trial evaluating BEV plus capecitabine in 49 patients with metastatic well-differentiated NETs (40 patients with small bowel carcinoids) demonstrated an overall disease control rate of 88% (with 18% partial response and 70% stable disease) [74]. In the most recent randomized controlled Phase III trial (SWOG [Southwestern Oncology Group] S0518 study), 427 patients with advanced well differentiated NETs with poor prognosis (progressive disease, refractory syndrome, grade 2 with more than six lesions, colorectal or gastric primary) were randomized 1:1 to either octreotide LAR 20 mg im. q21 days with bevacizumab 15 mg/kg q21 days or IFN- α -2b 5 million units 3 days/week. There was no significant difference in PFS in between the two arms (16.6 vs 15.4 months, HR: 0.93; 95% CI: 0.73–1.18; $p = 0.55$). However, interpretation of true activity of either agent is limited due to lack of a placebo-controlled arm. Furthermore, patients in both arms had significant toxicities with the most common grade 3 AEs being hypertension in the bevacizumab arm (31.5%) and fatigue (25.8%) and neutropenia in the IFN arm (11%) – it is unlikely that there will be further development of either agent in this setting but remain as options in consensus guidelines [75]. In practice, use of bevacizumab for this indication is often limited by reimbursement issues and we prefer to limit its use only as part of research protocols.

• VE GF tyrosine kinase inhibitors

Sunitinib is an oral tyrosine kinase inhibitor against VEGF_{1, 2, 3} and PDGFR- α and - β . Although studies have shown benefits of sunitinib in pancreatic NET [76], randomized trials to support its use in midgut neuroendocrine tumors are lacking. Currently, the SUNLAND study evaluating sunitinib versus placebo in combination with LAN in patients with advanced/metastatic midgut carcinoid tumors is ongoing (NCT01731925). Another study of mutation-targeted therapy with sunitinib or everolimus in patients with advanced low- or intermediate-grade GEP-NETs with or without cytoreductive surgery is underway (NCT02315625). Therefore, use of sunitinib in MNETs cannot be supported at this time and is pending the results of ongoing trials. Pazopanib is a tyrosine kinase inhibitor with activity against VEGFR_{1, 2, 3}, PDGFR- α and β and c-KIT that was investigated in 52 patients with GEP-NETs including 20 patients with carcinoid tumors. Although no radiographic responses

were noted in carcinoid patients, pazopanib was generally well tolerated with a median PFS of 12.2 months and overall survival (OS) of 18.5 in these cohort months [77]. The PAZONET study randomized 44 patients with advanced carcinoids including 15 with gastrointestinal carcinoids. The median PFS in the gastrointestinal cohort was 10 months [78]. This agent is currently being evaluated in an ongoing, placebo-controlled randomized Phase II study (NCT01841736). Sorafenib, another tyrosine kinase inhibitor that blocks VEGFR₂ and PDGFR- β was evaluated in a Phase II study of 93 patients including 50 with carcinoid tumors by Hobday *et al.*, in which a modest response rate of 10% was noted but with 43% of the patients experiencing grade 3 or 4 toxicities [79].

• Cytotoxic agents

Small intestine NETs are typically resistant to systemic chemotherapy in comparison to pancreatic NETs and therefore the role of chemotherapy in midgut neuroendocrine tumors remains controversial. Data supporting the use of cytotoxics is sparse and is mainly based on retrospective and small Phase II studies. In one study performed by Kulke *et al.*, in patients with metastatic NETs (which included 14 patients with well-differentiated carcinoid tumors) response rate to thalidomide and temozolomide was reported in only one patient (7%) [76]. A subsequent Phase II clinical trial of 34 patients with GEP-NETs who received BEV and temozolomide demonstrated no radiographic response in seven patients with small bowel carcinoid tumors [71]. Several theories have been put forth for this lack of activity: midgut neuroendocrine tumors are usually slow growing and therefore less sensitive to cytotoxic agents which target DNA synthesis. They also usually express higher level of the DNA repair enzyme α (6)-methylguanine DNA methyltransferase (MGMT), which protects tumor cells against chemotherapeutic agents such as temozolomide [80]. Variable response rates of 16–44% to streptozocin (STZ)-based regimen (mainly in combination with fluorouracil) have been described in prior studies [81–83]. Per current NCCN guidelines, for patients with progressive disease, and for whom no other treatment options are available, antineoplastic agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin and temozolomide may be considered [14].

Recent developments

• Telotristat etiprate

Telotristat etiprate targets the conversion of tryptophan to serotonin by blocking the enzyme tryptophan hydroxylase in peripheral tissues. Telotristat etiprate is the first oral medication developed for the treatment of carcinoid syndrome. In a preliminary prospective, placebo-controlled dose escalating study by Kulke *et al.*, in 23 patients whose diarrhea had not been controlled with stable dose of octreotide-LAR, 56% reported adequate relief of symptoms in the first 4 weeks and 50% had reduction in urinary 5-HIAA. Adverse effects were usually mild and transient (mainly gastrointestinal such as nausea, vomiting, abdominal discomfort and transaminitis) [84]. Two Phase III, randomized, placebo-controlled, double-blind studies with Telotristat etiprate were subsequently initiated: TELECAST (NCT02063659) and TELESTAR (NCT01677910). In a report of TELESTAR, which was presented at the European Cancer Congress, telotristat etiprate illustrated promising results. In this three-arm study, 135 patients with poor symptomatic response to octreotide-LAR were randomized to

placebo, telotristat 250 mg three-times a day (t.i.d.) or telotristat 500 t.i.d. over a 12-week period. All patients were continued on SSA for the entire study period. Patients received treatment with telotristat had statistically significant reduction in the number of daily bowel movements ($p < 0.001$). Telotristat etiprate showed an average reduction of 1.71 bowel movements per day (29%) at the dose of 250 mg, and an average reduction of 2.11 bowel movements per day (35%) at the dose of 500 mg while placebo group had decrease of 0.87 bowel movements per day (17%). In addition, greater proportion of patients on this medication (44% of patients receiving 250 mg and 42% of patients receiving 500 mg) achieved a durable response defined as at least a 30% reduction in daily bowel movements for at least half the days of the study period. Both regimens resulted in statistically significant decreased in urinary 5-HIAA level. Patients who received telotristat also experienced a lower frequency of flushing episodes and less intense abdominal pain compared with placebo, though these differences did not reach statistical significance. Overall both regimens of telotristat etiprate showed acceptable tolerability profile (the 250 mg dose was better tolerated in comparison to 500 mg in terms of gastrointestinal discomfort and mood), and adverse event profile was similar in all three groups. The trial is ongoing as 36-week open-label extension and further results are yet to be reported [85].

• PRRT

PRRT is a novel treatment modality, which was developed by using somatostatin receptors as targets to deliver cytotoxic radioactive agents. In this method, a radioactive isotope – typically a β -emitting agent – is chelated to a somatostatin analog (most commonly an octreotide derivative). Following administration to the patient and uptake by tumor cells, it leads to local antitumor effects. Generally well-differentiated tumors (low and intermediate grade) NETs with positive octreoscans are ideal candidates for PRRT [86]. Currently, yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu) are used as radioactive isotopes and the chelator of choice is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). Both are β -emitting agents. ^{90}Y has higher energy, shorter half-life and greater tissue penetration (~64 h/12 mm) in comparison to those of ^{177}Lu (160 h/2 mm, respectively). In prior studies, ^{90}Y -DOTA-tyr3-octreotide (aka ^{90}Y -DOTATOC, ^{90}Y -SMT 487 or ^{90}Y -edotreotide) was well tolerated and the overall response rate was reported to be 25–30%. Nephrotoxicity was noticed to be the major dose-limiting complication requiring concomitant aminoacid infusion [87–91]. Valkema *et al.* investigated ^{90}Y -DOTA on 58 patients (30 with MNET) and observed minimal to partial improvement in disease status in 57% ($n = 33$) of patients [92]. ^{90}Y -DOTATOC was also used in a single-arm multicenter Phase II study of 90 patients with progressive and octreotide-refractory NETs (24 patients had small intestine carcinoid tumors). In this study, ^{90}Y -DOTATOC resulted in median PFS of 16.3 months. Patients with improvement in diarrhea had statistically greater median PFS. Most common adverse events were gastrointestinal (nausea (57.8%), vomiting (46.7%), abdominal pain (21.1%)) which could be related to coadministration of amino-acids [93]. ^{177}Lu is a fairly newer agent and has been applied in the treatment of NETs since 2000 [94,95]. In one of the largest retrospective studies of ^{177}Lu performed by Kwekkeboom *et al.*, of 310 patients with GEP-NET, 45% of patients were reported to have some degree of response (minimal to complete) and 35% had stable disease following four treatment cycles with cumulative dose of 750–800 mCi (27.8–29.6 GBq) [94]. A Phase II study of ^{177}Lu on 32 patients (20 with MNET)

treated in the USA with repeated cycles of 200 mCi (7.4 GBq) up to cumulative dose of 800 mCi (29.6 GBq), demonstrated minimal to partial response in 31% and stable disease in 41% of patients. Treatment with multiple cycles was tolerated well with no significant hemo- or nephrotoxicity and significant improvement in quality of life and symptoms in all evaluable patients was also reported [96]. Most recently, the results for NETTER-1 study comparing high dose octreotide-LAR (60 mg) with PRRT (^{177}Lu -DOTA,Tyr-octreotide) in patients with inoperable, progressive, somatostatin receptor positive MNETs were presented at the European Cancer Congress, 2015. According to the report, Lutathera 7.4 GBq administered every 8 weeks (for 4 doses) significantly improves PFS ($p < 0.0001$, HR: 0.21; 95% CI: 0.13–0.34). Median PFS in Lutathera arm was not reached yet while the median PFS in the octreotide-LAR arm was 8.4 months. Data on safety profile although incomplete appear to be consistent with prior studies on Lutathera [97].

• mTor inhibitors (everolimus)

The mTOR is an intracellular serine/threonine kinase that participates as the central node of multiple signaling pathways (including IGF, EGF and VEGF) and regulates cell growth, proliferation, apoptosis, metabolism and angiogenesis [98]. Over activation of these pathways has been reported in NETs [99] and targeting mTOR demonstrated significant growth inhibition in preclinical models [100]. The RADIANT-2 study accrued 429 patients with progressive functional NETs (including 224 patients with small intestine carcinoid). Patients were randomized to placebo or everolimus 10 mg p.o. daily (in combination with octreotide-LAR in both arms). Based on central review, the combination arm had a trend toward clinically meaningful improvement in the primary end point of PFS (16.4 vs 11.3 months; HR: 0.77) that did not meet predefined boundaries for statistical significance. This could be related to multiple factors including imbalances between the two arms and also informed censoring with loss of events due to discrepancies in radiographic assessment between local and central reviews [101]. Most recently, the RADIANT-4 trial evaluating everolimus plus best supportive care versus placebo plus best supportive care randomized 302 patients (24% with small bowel/ileal tumors) with advanced, nonfunctional, nonpancreatic NETs 2:1 to everolimus vs placebo. The investigators found a significant improvement in the primary end point of PFS with everolimus therapy (11 months vs 3.9 months, HR: 0.48; 95% CI: 0.35–0.67; $p < 0.00001$). At the first interim OS analysis with 37% of information fraction, there was a trend toward improvement for therapy with everolimus. The safety profile was in line with prior studies of everolimus with the most common reported adverse events grades 1/2 being stomatitis, diarrhea, peripheral edema, fatigue and rash. The most common treatment-related adverse events grade 3/4, in everolimus and placebo arm, respectively, were stomatitis (9 vs 0%), diarrhea (7 vs 2%) and infection (7 vs 0%) [102]. The promising results of this study support the use of everolimus in advanced nonfunctional NETs of lung or GI origin including MNETs.

Conclusion & future perspective

MNETs are malignancies with distinctive characteristics which make their management challenging. Conventional antineoplastic agents have limited role given their slow-growing property and their role continues to be limited and SSA are the mainstay of tumor and

hormone control. For the next few years, while long-acting somatostatin analogs are expected play a central role in the management of these tumors, the approval of mTOR inhibitors and PRRT will likely expand the treatment landscape. Likewise, multiple Phase II clinical trials evaluating VEGF tyrosine kinase inhibitors (sorafenib and pazopanib) in MNET are ongoing. For symptomatic patients, emergence of the novel drug class (tryptophan hydroxylase) is the start of a new era in management of carcinoid syndrome. Additional studies are required to determine the most beneficial combinations of new agents and older drugs in order to improve the response rate and to define the most effective sequential order of therapies. Further investigations are also required to personalize therapeutic options and provide the promise of precision medicine to patients with NETs.

Conclusion

Figure 1 demonstrates our proposed updated algorithm to management of MNET. Key Phase III clinical trials have been summarized in Table 4.

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Practice points

- Management of midgut neuroendocrine tumors (MNETs) is based on multiple factors such as stage, grade, extent of disease, presence of carcinoid syndrome symptoms, performance status and organ function.
- Surgery is considered the only curative measure for patients with resectable disease.
- Currently, there are not enough data to support the role of adjuvant therapy following complete resection.
- Surgical resection of an asymptomatic primary and debulking of liver metastases in patients with advanced disease are areas of debate and controversy.
- For some asymptomatic patients with metastatic, unresectable NETs but with low tumor burden, 'wait and see' policy may be appropriate.
- In patients with liver predominant disease, liver-directed therapy including ablation, radioembolization, bland embolization and/or chemoembolization maybe considered.
- Systemic therapy may be indicated for tumor and/or carcinoid syndrome symptom control.
- Somatostatin analogs (SSA) have long been the mainstay of treatment of carcinoid syndrome and dosage maybe increased as required for optimal symptom control.
- Two placebo-controlled, Phase III trials have established the role of SSA (octreotide, PROMID and lanreotide, CLARINET) in tumor control of MNETs.
- Octreotide and lanreotide appear to have similar safety and efficacy profiles and are often the first line in the management of metastatic/ unresectable MNET.
- There have been major developments recently in management of MNETs with three major positive Phase III trials whose results will likely change management of MNETs.
- TELESTAR: This trial established the efficacy of the peripheral tryptophan hydroxylase inhibitor, telotristat etipratecan in management of SSA refractory carcinoid syndrome.
- RADIANT 4: This trial established the role of the mTOR inhibitor, everolimus in the treatment of progressive, advanced, nonfunctional, nonpancreatic lung and gastrointestinal neuroendocrine tumors including MNETs.

- NETTER-1: The first randomized trial of PRRT, peptide receptor radionuclide therapy (^{177}Lu -DOTATATE) showed significant improvement in progression-free survival of patients with advanced, progressive, SSA refractory, octreoscan-positive MNET over high-dose octreotide LAR.

Figure 1.

Proposed approach for the treatment of well-differentiated midgut neuroendocrine tumors. MNET: Midgut neuroendocrine tumor; RFA: Radio-frequency ablation; SSA: Somatostatin analogs; TACE: Transarterial chemoembolization; TAE: Transarterial embolization.

Table 1

Grading of gastrointestinal neuroendocrine tumors

Differentiation	Grade	Ki-67 index	Mitotic index (mitoses/10 HPF)
Well differentiated	G1 (low grade)	<2%	<2
	G2 (intermediate grade)	3–20%	2–20
Poorly differentiated	G3 (high grade)	>20%	>20

HPF: High-power field.

Data taken with permission from AJCC [12] and ENETS [11].

Table 2

TNM staging system for small bowel neuroendocrine tumors.

Primary tumor (T)	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 1 cm or less
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa
T4	Tumor invades visceral peritoneum (serosa) or invades other organs Add (m) for multiple tumors
Regional lymph nodes (N):	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastases (M):	
M0	No distant metastases
M1	Distant metastasis

Data taken with permission from AJCC [12] and ENETS [11].

Table 3

TNM staging system for small bowel neuroendocrine tumors.

Stage	T	N	M
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

Data taken with permission AJCC [12] and ENETS [11].

Table 4

Key Phase III clinical trials in midgut neuroendocrine tumors.

Category	Trial name	Study (year)	Patient population	Study arms	Patients (n)	HR p-value	Results of primary end-point	Ref.
Somatostatin analogs	PROMID	Rinke (2009)	Metastatic functional and nonfunctional MNET	Octreotide-LAR 30 mg im. monthly	42	HR: 0.34	mTTP: 14.3 months	[36]
	CLARINET	Caplin (2014)	Metastatic, well-mod differentiated, SSA receptor positive, nonfunctioning NETs (pNET, midgut, hindgut, unknown)	Placebo Lanreotide 120 mg sc. monthly Placebo	43 101 103	p = 0.000072 HR: 0.47 p < 0.001	mTTP: 6 months mPFS: Not reached mPFS: 18 months	[15]
PRRT	NETTER-1	2015	Metastatic, MNETs/progressive on baseline dose of SSA	PRRT (¹⁷⁷ Lu-DOTATATE [Lutathera] 7.4 GBq q8w × 4 doses) + octreotide-LAR 30 mg q4w Octreotide-LAR 60 mg/day	116 113	HR: 0.21 p < 0.0001	mPFS: Not reached mPFS: 8.4 months	[97]
Targeted therapy	RADIANT-2	Pavel, (2011)	Progressive functional NETs	Everolimus 10 mg/day + octreotide-LAR	216	HR: 0.77	mPFS: 16.4 months	[101]
	RADIANT-4	Yao (2015)	Advanced, well-differentiated, nonfunctional, GI and lung NETs	Placebo + octreotide-LAR Everolimus 10 mg/day+ best supportive care	213 205	p = 0.026 HR: 0.48	mPFS: 11.3 months mPFS: 11 months	[102]
	SWOG S0518	Yao (2015)	Metastatic, unresectable, well-differentiated (G1,G2), GI-NET (foregut, midgut, hindgut)	Placebo + best supportive care Bevacizumab + octreotide-LAR IFN-α-2b + octreotide-LAR	97 197 194	p < 0.00001 HR: 0.93 p = 0.55	mPFS: 3.9 months mPFS: 16.6 months TTF: 9.9 months mPFS: 15.4 months TTF: 5.6 months	[75]
	TELESTAR	Kulke (2015)	Carcinoid syndrome not adequately controlled with SSA	Telotristat etiprate 250 mg + SSA Telotristat etiprate 500 mg + SSA Placebo + SSA	135	p < 0.001	29% reduction in number of bowel movements 35% reduction in number of bowel movements 17% reduction in number of bowel movements	[85]

HR: Hazard ratio; im.: Intramuscular; Lu: Lutetium; MNET: Midgut neuroendocrine tumor; mPFS: Median progression-free survival; NET: Neuroendocrine tumor; pNET: Pancreatic neuroendocrine tumor; PRRT: Peptide receptor radionuclide therapy; q4w: Every 4 weeks; q8w: Every 8 weeks; QoL: Quality of life; sc.: Subcutaneous; SSA: Somatostatin analog; TTF: Time to treatment failure.