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Pharmacotherapy of Zollinger-Ellison syndrome

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Abstract

Introduction—Pharmacotherapy in the management of patients with ZES is often equated with the medical management of the acid hypersecretion. However, pharmacotherapy is also increasingly involved in the other management areas of these patients.

Areas covered—This paper reviews the role of pharmacotherapy in all aspects of the management of patients with ZES. Newer aspects are emphasized. This includes the difficulty of diagnosing ZES in patients taking proton pump inhibitors. Also covered is pharmacotherapy in the control of acid hypersecretion; in controlling other hormonal hypersecretory states these patients may develop, including the hyperparathyroidism in patients with MEN1 and ZES; pharmacotherapy involved in tumor localization; and pharmacotherapy involved in the treatment of advanced metastatic disease. The latter includes chemotherapy; liver-directed therapies; biotherapy (somatostatin/interferon); peptide radio-receptor therapy; and molecular targeted therapies including the use of mTor inhibitors (everolimus) and tyrosine kinase inhibitors (sunitinib).

Expert Opinion—Pharmacotherapy is now involved in all aspects of management of patients. The result of this is that ZES has progressed from where it initially was entirely a surgical disease to the present where medical treatment plays a major role in almost all aspects of the management of these patients.

Keywords

acid hypersecretion; chemotherapy; gastrinoma; pancreatic endocrine tumor(PET); Multiple Endocrine Neoplasia type 1(MEN1); neuroendocrine tumor(NET); peptide radioreceptor therapy(PRRT); proton pump inhibitor(PPI); Zollinger-Ellison syndrome(ZES)

1. Introduction

Zollinger-Ellison syndrome (ZES) is caused by gastric acid hypersecretion characteristically resulting in severe gastroesophageal peptic ulcer disease, which is due to the ectopic secretion of gastrin, by a neuroendocrine tumor (gastrinoma), usually present in the duodenum or pancreas[1–4]. Many often use the terms gastrinoma and ZES interchangeably, although historically ZES refers to the overall clinical syndrome and gastrinoma to the

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9. Pharmacotherapy of patients with gastrinomas-Declaration of Interest.

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presence of a neuroendocrine tumor (NET) secreting gastrin[5,6]. Gastrinomas are historically classified as belonging to the pancreatic endocrine tumor (PET) family of disorders, which include nine different types of neuroendocrine tumors[2,6,7]. PETs include NETs associated with a clinical syndrome due to specific hormone overproduction [insulinomas; glucagonomas; VIPomas, GRFomas; somatostatinomas; pancreatic NETs causing Cushing's syndrome (ACTHomas), carcinoid syndrome or hypercalcemia(PTHrp-omas), also including a few very rare syndromes (PETs secreting renin, luteinizing hormone, erythropoietin)] as well as PETs not causing a specific hormonal syndrome, but frequently secreting peptides which are clinically silent (pancreatic polypeptide, chromogranin A, neuron-specific-enolase, etc)(PPomas, nonfunctional PETs[NF-PETs])[7,8]. Whereas PETs are closely related to carcinoids and both are classified as neuroendocrine tumors, sharing mainly pathological features and some similarities in biological behavior, they are generally subclassified separately with recent studies showing they have a different pathogenesis, respond differently to various antitumor therapies and often behave differently biologically[7,9].

Gastrinomas, as other functional PET syndromes have two important treatment aspects and both must be dealt with: the control of the hormone-excess state as well as treatment directed at the PET (gastrinoma itself)[6,7,10,11]. These aspects must both be considered separately frequently, because the only single treatment that would resolve both problems is the successful surgical resection of the gastrinoma, however this is possible in <50% of all patients long-term with sporadic ZES, and no patients with MEN1/ZES, unless aggressive resections such as Whipple resections are performed [6,12–16]. This occurs because 70–90% of gastrinomas are malignant and in various series 20–40% of patients present with unresectable liver metastases; furthermore, only 60% of potentially resectable gastrinomas in patients with sporadic disease are cured long-term because at surgery 40–70% already have lymph node metastases[16–18]. Furthermore, 20–30% of patients have ZES as part of the Multiple Endocrine Neoplasia-type 1 syndrome (MEN1), an autosomal dominant disorder due to mutations in an 11q13[19–24]. These mutations cause alterations in a 610 amino acid protein, menin, which results in hyperplasia/tumors of multiple endocrine (pituitary, parathyroid, adrenal) and nonendocrine tissues (carcinoids-lung, thymus, gastric ECL cells, tumors of the skin, CNS, smooth muscle)[19–24]. The gastrinomas in most MEN1 patients with ZES are multiple, duodenal in location, frequently small (<0.5 cm), and associated with lymph node metastases in 40–70% [7,8,12,14–19,21]. Because of these features, gastrinomas in MEN1/ZES patients, in contrast to patients with ZES without MEN1 (Sporadic ZES), are rarely curable without aggressive surgical resections such as a Whipple procedure [7,8,12,14–19,21], which is not routinely recommended. Therefore life-long treatment of both the acid hypersecretion and gastrinoma as well as other PETs is needed in almost all MEN1/ZES patients[8,12,15,17,19,21,25,26].

This paper reviews the role of pharmacotherapy in the diagnosis and management of ZES. Pharmacotherapy is involved and has to be taken into consideration in all steps in the management of patients with ZES including: suspecting the diagnosis; establishing the diagnosis; diagnosing the possible presence of MEN1; treating the acid hypersecretion as well as hypersecretion of other hormonal states in some ZES patients (i.e. Cushing's, carcinoid syndrome; an insulinoma in MEN1 patients with ZES, etc); tumor localization; management during surgical procedures; treatment of aspects of MEN1 if present and treatments directed at the tumor in patients with advanced disease. This review will concentrate on current practices and newer aspects and not review all aspects of pharmacotherapy in ZES because pharmacotherapy in a number of these areas of management has recently been reviewed. This includes the pharmacotherapy of treatment of acid hypersecretion in ZES patients[4,11, 27,28]; a review of diagnosis of ZES[4,29–34]; general management of ZES[4,11]; surgical management of ZES[16,25,35,36] and the

treatment of advanced disease in patients with ZES and other PETs or gastrointestinal NETs[36–41]. The latter include reviews of targeted therapies with mTor inhibitors[36,37,39,42,43], tyrosine kinase inhibitors[36,37,39,42], somatostatin analogues[36,37,39,44,45]; liver-directed therapies and peptide radio-receptor therapy (PRRT)[36,37,39,46–50]; surgical debulking/cytoreduction[35–37] and chemotherapy[36,37,39].

2. Pharmacotherapy and suspect ZES

For ZES to be diagnosed it has to be first suspected. The diagnosis is very frequently missed early in the disease course with a mean delay in diagnosis in various studies of 5–8 years[3] and even in patients with MEN1, in which ZES is the most common functional PET syndrome[19,21], the diagnosis is frequently delayed a mean of 5 years[22]. Pharmacotherapy can contribute to this delay in diagnosis and in fact, studies provides evidence that it is increasingly contributing to a delay as well as increasing the difficult in making the diagnosis[4,29–31,51,52]. The latter aspect will be discussed in the next paragraph. One study[51] demonstrates that since the widespread use of proton pump inhibitors (PPIs)(omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole) the number of possible ZES cases referred to well two established centers, one in the United States[NIH] and the other in Rome, has decreased. This decrease was ascribed[51] largely to the fact that the disease was less often suspected since the widespread use of PPIs. PPIs, because of their long duration of action (lasting>3–4 days) cause potent, prolonged inhibition of gastric acid secretion in almost all normals and patients with various diseases, including those with ZES[4,10,11,27,28, 29,53–59]. Prior to PPIs, histamine H₂- receptor antagonists (primarily cimetidine, ranitidine, famotidine) were widely used to treat gastroesophageal reflux(GERD) and peptic ulcer disease (PUD) in both patients with[11,58,60–63] or without ZES[64]. Histamine H₂-receptor antagonists have a significantly shorter duration of action than PPIs (<8–15 hours) and cause less potent inhibition of acid secretion than PPIs[62,64,65]. Consistent with their lower potency, subsequent studies demonstrated that the acid hypersecretion in most patients with ZES was not controlled long-term with the conventional doses of histamine H₂-receptor antagonists used in patients without ZES[60–62,65], whereas this was not the case with PPIs[10,27,56,66,67]. The result of this was that many patients were suspected as having ZES when their symptoms/ GERD/PUD were not controlled by conventional doses of histamine H₂-receptor antagonists, while this occurred much less frequently with PPIs[10,27,56,66,67]. This delay in diagnosis by the use of PPIs can result in a delay in treatment which is likely to prove particularly important to patients with advanced disease who are increasing dying from tumor progression [7,8,12,18,37,51]. At present in this era of PPIs, ZES should be suspected in any patient with a history of severe PUD/GERD disease; PUD in unusual locations; with prominent gastric folds on endoscopy because these occur in 92% of ZES patients[3]; with a history of endocrinopathies; H. pylori negative PUD[68]; family history of PUD; PUD with diarrhea or the presence of hypergastrinemia while not taking PPIs[4,10,62].

3. Pharmacotherapy and diagnosis of ZES

Pharmacotherapy is involved in two aspects in the diagnosis of ZES. First, as mentioned above the widespread use of PPIs has greatly complicated the diagnosis of ZES, not only because PPIs control acid hypersecretion in most patients with ZES with conventional doses [56], but also because their use leads to hypergastrinemia in up to 80–100% of normal subjects as well as patients with idiopathic GERD or PUD in a number of series[4,29,31,34,69–72]. Therefore, while the patient is taking PPIs, hypergastrinemia could be due to the presence of underlying ZES (uncommonly) or to the use of the PPI itself

resulting in physiological hypergastrinemia due to the hypo-/achlorhydria induced by its long-term use. Second, secretin provocation tests are needed in some patients to make the diagnosis of ZES[32]. In the past calcium infusions were used or meal testing but these are rarely used at present[32,62,73]. In some countries where secretin is not available, it has been proposed a glucagon stimulation test could be used[74].

Assessment of fasting serum gastrin levels is the initial study usually performed when ZES is suspected[8,27,31,33,75]. This approach is taken, because except in special, uncommon circumstances (postgastrinoma resection[75], MEN1/ZES patients postparathyroidectomy[76]), >98% of ZES patients have an elevated fasting serum gastrin when initially diagnosed[33]. Therefore, because PPIs so frequently can cause hypergastrinemia themselves in ranges that overlap with that seen in ZES and are so widely used, the only way to be certain the hypergastrinemia is not due to the PPI, is to stop the PPI, however, this can lead to severe PUD/GERD complications if not done carefully[29,30,34]. Because of these risks, one recent study[30] has proposed that the diagnosis of ZES should be made by not stopping the PPI and instead an attempt be made to establish the diagnosis by identifying other manifestations of ZES (i.e., PET, prominent gastric folds, etc) that would support the diagnosis. Unfortunately, as pointed out in two recent papers[29,34], this latter approach is frequently not possible in many patients with ZES, especially early in their disease course. Furthermore, as discussed below, PPIs can also lead to a false positive secretin provocative test[77], so this approach cannot be used to diagnose ZES on PPIs. The above study [30] also proposes that if the diagnosis can not be made by not stopping the PPI then an attempt should be made by titrating the PPI dose downward and retesting. This approach has not been systematically studied, however it may not be possible not to achieve an acidic pH (<2) in many patients because they are well controlled on even the lowest omeprazole dose [56]. It is therefore recommended that when ZES is suspected the patient should be referred to a center with expertise in making the diagnosis and with familiarity with the potential risks of stopping PPIs[29,34].

Whereas 40% of ZES patients initially have a fasting serum gastrin level off of PPIs >10 fold elevated and their diagnosis can be established by demonstrating the presence of a gastric pH<2[2,4,10,33], however 60% have fasting gastrin levels elevated<10-fold and the presence of a gastric pH<2[2,4,8,10,12,31,33,78], findings which overlap with a number of other diagnoses (H. pylori infections, antral G cell syndromes, gastric obstruction, etc)[4,32] and thus are not specific for ZES. Therefore the secretin provocative test is recommended in this group to establish the diagnosis[4,8,12,78]. In the US at present the secretin test is performed using synthetic human secretin (ChiRhoStim, Inc., Burtonsville, MD) with a recommended bolus intravenous dose of 0.4 mcg/Kg-body weight[79]. A recent detailed review of secretin testing in ZES demonstrates the best criterion for a positive response is an increase in fasting serum gastrin postsecretin injection of 120 pg/mL which has a sensitivity of 94% and specificity of 100%[32] when the test is performed off of PPIs. Most studies support the conclusion that the exaggerated increase in fasting gastrin levels in patients with ZES postsecretin injection is due to the direct interaction with secretin receptors on the gastrinomas[32,80]. This conclusion is supported by results from a number of studies which demonstrate secretin receptor mRNA/receptor and /or receptors on gastrinoma cells, as well as the ability of secretin to stimulate gastrin release from dispersed gastrinoma cells *in vitro*[32,80].

4. Pharmacotherapy and control of acid hypersecretion or other hormone-excess states in ZES

4A. Pharmacotherapy and control of acid hypersecretion-General

Gastric acid hypersecretion is a hallmark of ZES with mean basal secretory rates >4-times normal (41.7 mEq/hr)[2] and with basal secretory rates up to 12 times normal in individual patients[2,5]. A large number of studies have demonstrated that the gastric acid hypersecretion must be controlled both acutely and long-term in ZES patients and if it is not, severe complications of GERD/PUD almost invariably developed which were very frequently fatal[1,4,5,62].

Initially only total gastrectomy was effective at controlling the gastric acid hypersecretion[1,5,62], however with the development of histamine H₂-receptor antagonists and later, PPIs, medical control is now possible in almost every patient[4,10,28,59,62,66,67,81], except for the rare patient who cannot or will not take oral antisecretory drugs, hence total gastrectomy is now rarely needed[18,62,82]. Histamine H₂-receptor antagonists including cimetidine, ranitidine and famotidine have all been used to successfully control the gastric acid hypersecretion in ZES patients[4,11,61,65,81,83]. Comparative studies show that cimetidine; ranitidine; famotidine have a relative potency of 1:3:32 on a milligram basis for inhibiting acid secretion in ZES patients and that ranitidine and cimetidine have the same duration of action, whereas famotidine has a 30% longer duration of action, allowing in some patients less frequent dosing[65]. To control the acid in ZES patients, high, frequent (q4–6 hourly) doses are frequently required with all histamine H₂-receptor antagonists with mean daily doses of 4.9, 2.2, and 0.33 grams for cimetidine, ranitidine and famotidine, respectively in the long-term NIH studies[62]. Despite these high, frequent histamine H₂-receptor antagonist doses, these drugs were generally free of dose-related side-effects except for anti-androgen side-effects with cimetidine (gynecomastia, impotence)[61,62,65,81,83] and were effective long-term, although on the average at least one dosage increase was required per year[61,62,65,81,84]. Vagotomy (complete or selective) can also reduce acid hypersecretion and could result in lower doses of histamine H₂-receptor antagonists [5,58,62,], however with the availability of PPIs it is rarely used at present.

PPIs because of their long duration of action and potency, which allow once a day dosing in most patients, are now the drugs of choice for treating the acid hypersecretion in ZES patients[4,11,12,27,28]. Each of the PPIs has been shown to be effective in ZES patients including omeprazole[27,56,66,81], lansoprazole[11,27,59,67], esomeprazole[27,55,85,86], rabeprazole[27,53,87], and pantoprazole[27,88,89]. PPI's have remained effective in long-term studies for up to 10 years with no evidence of tachyphylaxis[66,67,81].

Long-term PPI treatment in ZES has proven safe with very few patients (<0.1%) having to stop treatment because of any side effect. The long-term effects of PPI-induced hypo-/achlorhydria have been a potential concern especially related to the possible malabsorption of nutrients requiring gastric acid secretion (vitamin B₁₂, iron, calcium), as well as the possible effect of enhanced hypergastrinemia, resulting in a possible increased development of gastric carcinoid tumors or other neoplasms[57,90,91]. Low vitamin B₁₂ levels are not infrequent in ZES patients[92,93] and one study[92] demonstrated that it was more frequent in patients treated with PPIs as well as demonstrating that low vitamin B₁₂ levels correlated with the presence of PPI-induced hypochlorhydria, whereas a second study[93] did not show this association. No deficiency in body iron with long-term PPI in ZES patients was found[94]. Recently evidence has been provided from correlative studies or epidemiological studies, that long-term PPI treatment results in an increased incidence of bone fractures,

particularly of the hip or spine[91,95], but there are no specific studies on ZES patients demonstrating such an occurrence. There are a number of reports of lansoprazole-included colitis in patients with various diseases in the literature[96], but none in any patients with ZES. Similarly chronic PPI treatment is reported to be associated with the development of community-acquired pneumonias, hypomagnesemia, enteric infections, and interstitial nephritis[91,97,98], however there are no reports in ZES patients treated long-term with PPIs, even though in many cases the patients were treated with higher than conventional doses. Prolonged hypergastrinemia in animals and in man results in proliferation of the enterochromaffin-like cells (ECL-cells) of the gastric mucosa and in numerous animal models in which chronic hypergastrinemia is induced, gastric carcinoid tumors (ECLomas) develop, some of which are malignant[90,99]. In patients with ZES, >90% of patients demonstrate ECL-cell proliferation, however those with the sporadic form of ZES (non-MEN1) rarely develop gastric carcinoid tumors[99,100], however they occur with >70 higher frequency in patients with MEN1/ZES with 23% having gastric carcinoids in one study and in 10–30% they can be malignant[23]. There are no reports that the treatment with PPI's accelerates the development of these gastric carcinoid tumors, perhaps related to the fact that ZES patients have hypergastrinemia already due to the gastrinoma and if the acid treatment is appropriately monitored in many cases the fasting gastrin levels do not change. Some studies propose that hypergastrinemia is associated with increased development of colonic cancer[90,101], but in one study of ZES patients no increase in the occurrence of colonic neoplasms was found[90].

There is no general agreement on the best protocol to start the use of PPIs. In the center with the largest experience (NIH) it is recommended in uncomplicated disease (see next paragraph for definition) that patients be started on a dose equivalent to omeprazole 60 mg/day and that it can be decreased with time [4,5,7,8,12,27,57,58,66, 84]. The ideal is to titrate the dose using acid output but few now have this capability. Symptom control (particularly diarrhea, pain) can be used and if mucosal disease is present repeat examination should be performed after 4–6 weeks. In patients with complicated disease higher doses are required as outlined in the next paragraph [21,56,60,66,76,103].

Somatostatin analogues (Octreotide, Lanreotide) inhibit the release of gastrin from the gastrinoma and can also control gastric acid hypersecretion[28]. However, because parenteral administration is required, and because the oral PPIs are so effective, somatostatin analogues are rarely used in ZES to control the acid hypersecretion[28]. Somatostatin analogues are increasingly used for their anti-tumor growth effects in patients with advanced disease and this will be discussed in a later section[36,37,39,44,45,102].

4B. Pharmacotherapy and control of acid hypersecretion in ZES-Specific situations: (complicated disease, pregnancy with ZES, use of parenteral therapy)

Gastric acid hypersecretion in ZES patients with complicated disease defined as those with moderate-severe GERD with or without esophageal strictures, previous acid-reducing surgery (particularly Billroth-2 operations) or with MEN1, especially with hyperparathyroidism that is not well-controlled, has been shown in number of studies to be more difficult to control[21,56,60,66,76,103]. In each case either higher doses or more frequent doses of histamine H₂-receptor antagonists are required and even with PPI's, higher doses and more frequent use of twice a day or rarely three times a day administration is required[21,56,60,66,103]. Studies demonstrate that if sufficient antisecretory drug is given to reduce gastric acid hypersecretion before the next drug dose to <10 mEq/hr (<5 mEq/hr if previous gastric acid-reducing surgery), PUD will heal, PUD complications averted, and new disease prevented, as well as the patient becoming asymptomatic[56,104]. However, patients with moderate-severe GERD or with previous Billroth-2 resections frequently require greater acid inhibition for mucosal healing with acid reduced to <1 mEq/hr before

the next dose if still symptomatic and repeat endoscopy to assess healing[56,60,66,76,103]. The hypercalcemia due to the hyperparathyroidism results in an increased resistance to antiseecretory drugs and therefore higher doses of PPIs and usually BID dosing is required until the it is adequately controlled[21,56,66,76]. This is usually accomplished by performing a 3.5 or 4-gland parathyroid resection with implant[76], although in some special cases, medical therapy with the calcium sensing receptor allosteric modulator, cincalcet is being used[105,106].

Until recently there was very little data to plan management of the gastric acid hypersecretion in pregnant females with ZES[107]. Various strategies were proposed[107] including attempted curative resection of gastrinoma prior to pregnancy; performing a parietal cell vagotomy prior to pregnancy to reduce the antiseecretory drug dose and perhaps need for antiseecretory drug administration; if the patient has MEN1/ZES with hyperparathyroidism then correcting the hyperparathyroidism can markedly reduce the dose of antiseecretory drug needed; the use of low dose ranitidine instead of cimetidine, because of cimetidine's anti-androgen effects and possibly the use of PPI's, for which there was little data available, until recently, to assess there possible safely in this situation[107]. Recently meta-analyses have concluded that the use of either oral histamine H₂-receptor antagonists[108,109] or PPIs[110,111] is safe during pregnancy. Their use during pregnancy was not associated an increased occurrence of congenital malformations, spontaneous abortions or preterm delivery, with the authors concluding that they can be used for the treatment of diseases such as ZES during pregnancy. Furthermore, two case studies report the delivery of normal babies in two patients with ZES treated with PPIs[112,113], one patient treated with omeprazole and the other with lansoprazole.

If patients can not take oral antiseecretory drugs, it is important to control the acid hypersecretion rapidly and until they can be resumed because PUD complications can develop rapidly. During these periods, parenteral administration of gastric antiseecretory drugs is often required in the course of treating patients with ZES[4,10,27,114–116]. Even though PPIs can have a long duration of action in an individual patient (>3 days), is not possible without careful previous studies to know the exact duration it is effective for a given patient, therefore for most major surgical procedures, parenteral antiseecretory drug administration to control the gastric hypersecretion is required, as well as during other illness when oral intake can not be maintained for a number of days. Studies show that parenteral histamine H₂- receptor antagonists can control acid hypersecretion in ZES for prolonged periods of time, however relative higher doses are required and a continuous intravenous administration is needed[58,114–116]. Studies show that parenteral PPI's (omeprazole, pantoprazole) can also control acid hypersecretion in ZES[54,88,117–119] and that because of their long duration of action; intermittent parenteral administration (every 8–12 hours) is effective and can control acid hypersecretion for extended periods without tachyphylaxis. At present in the US, intravenous preparations of PPI's that could be used in ZES include intravenous pantoprazole, esomeprazole and lansoprazole[119]. In one study [118] a starting dose of 80 mg of pantoprazole given by 15 min infusion every 8 hours was recommended because it controlled gastric acid hypersecretion in all ZES patients studied both acutely and up to 7 days.

4C. Pharmacotherapy and control of other hormone-excess states in patients with ZES[carcinoid syndrome, Cushing's syndrome, other functional PETs]

Patients with ZES, particularly those with MEN1/ZES, not infrequently develop another functional hormonal syndrome during their disease course[19,22,120–124]. The functional syndromes most commonly seen include Cushing's syndrome[121,122,125]; other functional PETs (insulinomas, glucagonomas, etc) especially in patients with MEN1[22,126]; tumor-mediated hypercalcemia[124] and rarely carcinoid

syndrome[123,127]. These are in addition to the development of hyperparathyroidism in almost all patients with MEN1 (discussed above)[22,128] and the development of functional pituitary syndromes (prolactinomas, acromegaly, Cushing's disease) in MEN1 patients[22]. These additional functional PET syndromes frequently require specific treatments, because in many cases the PETs may be advanced and unresectable. This is particularly true in the case of Cushing's syndrome, which when it occurs in ZES patients without MEN1, it is almost always associated with advanced metastatic disease and has a very poor prognosis[121,122,125]. In some cases surgical excision is effective at controlling the additional hormone excess state (insulinomas, especially in MEN1 patients)[14,129] and should be performed whenever possible. In most of the cases the appropriate pharmacotherapy is used to control these additional functional syndromes or in the case of advanced metastatic disease, anti-tumor treatments are used (discussed in a later section). This pharmacotherapy includes treatment of prolactinomas in patients with MEN1(dopamine agonists, surgery)[129]; the treatment of Cushing's syndrome (surgical or medical [ketoconazole, metyrapone, mitotane, etomidate, mifepristone, adrenalectomy]) [130]; treatment of functional PET syndromes or carcinoid syndrome with advanced disease with long-acting somatostatin analogues (octreotide-LAR, lanreotide-autogel) [36,37,39,44,45]; treatment of metastatic insulinomas with the mTor inhibitor, everolimus[8,131] and treatment of insulinomas with frequent feedings, diazoxide and occasionally somatostatin analogues prior to surgery[8,131].

5. Pharmacotherapy and tumor localization in ZES

Tumor localization is needed in all steps in the management of ZES including the need to assess tumor location, size, changes with time, tumor extent and changes with treatment during the course of the disease[7,8,78,132,133]. Pharmacotherapy contributes in some fashion in the performance of almost every tumor imaging modality used; in many cases functioning as a contrast agent. A large number of different imaging modalities are used for gastrinoma localization including cross-sectional imaging studies[computed tomography (CT), ultrasound, magnetic resonance imaging (MRI)][132,134], selective angiography[132], somostatin receptor scintigraphy (SRS) using radiolabeled somostatin analogues [In the US principally ^{111}In dium-penetreotide (Octreoscan)][132,135]; endoscopic ultrasound (EUS)[12,18], assessment of gastrin gradients either basally in the portal venous circulation or in the hepatic veins after secretin-provocation[136–138] and increasingly in many parts of the world, positron emission tomography using various somostatin labeled analogues [primarily ^{68}Ga -DOTA⁰, Tyr³-octreotide][8,49]. At surgery additional localization methods are used primarily aimed at localizing duodenal gastrinomas which are frequently small and difficult to find[8,16,139,140]. These include transillumination of the duodenum, intraoperative ultrasound, and full mobilization of the duodenum (Kocher maneuver)[13,16,140,141].

Gastrinomas, as are other PETs and NETs, are generally highly vascular tumors and thus are frequently best seen with contrast agents. During the triphasic CT scan various contrast agents are used with pre-contrast, contrast and post contrast assessment and during MRI, various gadolinium contrast agents are used[132,142,143]. Unfortunately, detection of gastrinomas, as with other PETs, is size dependent to a large degree and small lesions (< 1 cm), especially duodenal gastrinomas, are frequently missed on cross-sectional imaging studies[132,135,139,140]. Gastrinomas, as other NETs, frequently overexpress somatostatin receptors and this overexpression is now widely used to image these tumors as well as increasingly to treatment them by coupling various somostatin analogues to various radiolabeled compounds[49,132,135](see section below). In the US localization is primarily performed using [^{111}In -DTPA⁰]-octreotide (Octreoscan) which has been shown in a number of studies to be more sensitive than cross-sectional imaging when combined with SPECT

imaging for detection of both the primary tumor and their metastases, as well as also to have the advantage of allowing whole body imaging at one time[49,132,135,144,145]. Although not yet available in the US, recent studies demonstrate that positron emission tomography using various radiolabeled somatostatin analogues (primarily ^{68}Ga -DOTA⁰, tyr³]octreotide/octreotate) are even more sensitive and that their use will change management in a significant number of patients[49].

6. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas

6A. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: General

Patients with advanced metastatic gastrinomas, similar to with other PETs, have a significant decreased survival with the survival depending to a large degree on the extent of the metastatic disease as well as its rate of growth[121,133,146]. In patients with gastrinomas 10 year survival is 96% with no liver metastases, with development of any liver metastases is 85%, with liver metastases when first seen is 26%, with limited liver metastases at any time with one lobe involved is 78%, limited liver metastases with both lobes involved (<5 metastases/lobe) is 80% and with diffuse liver metastases at any time is 16%[121,146]. Furthermore, 30% of patients with liver metastases develop bone metastases at some point and this is a very poor prognostic factor with the mean time of death of 1.9 years and a 10-year survival rate of 15%[121]. Because gastrinomas are malignant in 60–90% of patients[5,146], if not cured surgically[147], a significant proportion of patients will require treatment directed at the gastrinoma itself with time now that the acid hypersecretion can be satisfactorily treated. There are a large number of different treatments proposed, and as mentioned earlier, many have been recently reviewed and thus will not be covered in detail in this review on pharmacotherapy. These include articles dealing generally with the treatment of advanced disease in patients with ZES and other PETs or gastrointestinal NETs[36–41]. The latter include reviews of targeted therapies with mTor inhibitors[36,37,39,42,43], tyrosine kinase inhibitors[36,37,39,42], somatostatin analogues[36,37,39,44,45]; liver-directed therapies; peptide radio-receptor therapy (PRRT) [36,37,39,46–48]; surgical debulking/cytoreduction[35–37] and chemotherapy[36,37,39].

6B. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: chemotherapy

In contrast to treatment of patients with advanced carcinoid tumors, chemotherapy continues to have a role in the treatment of advanced gastrinomas and other PETs[7,9,36,37,78,141,148]. In patients with well-differentiated metastatic PET/gastrinomas chemotherapy with streptozotocin in combination with 5-fluorouracil alone or with doxorubicin results in objective response rates of 20–40%, however complete response rates are uncommon, and the responses are generally not long-term (mean 5–20 months) [7,37,141,148]. Pharmacotherapy with streptozotocin combinations is associated with considerable morbidity (especially nausea/vomiting, renal toxicity). Recently[149], it is reported that the combination of capecitabine/temozolomide show promise with a partial response rate of 70% in 30 patients with advanced PETs, and this has lead to this regimen now being investigated in larger studies. Poorly differentiated gastrinomas/PETs (grade 3 with high proliferative indices[Ki67>20%, presence of nuclear atypia, necrosis]), characteristically show rapid growth with a poor prognosis[37,150,151]. The recommended treatment is cisplatin-based therapy combined with either etoposide alone or in combination with other drugs (paclitaxel, vincristine). This regimen result in remissions in 14–80% with a mean duration of <12 months.

6C. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: Biotherapy (Somatostatin analogues, Interferon)

Numerous basic studies and various clinical studies support the conclusion that both somatostatin analogues and interferon can have anti-growth effects on PETs and carcinoid tumors, as well as their antisecretory effects on ectopically secreted hormones/ amines[7,36,37,44,45,152]. In patients with metastatic midgut carcinoid tumors in a prospective, double-blind, placebo controlled study; octreotide LAR[153] extended the time to progression (14.3 vs 6 mos, $p<0.00008$) resulting in a 67% of patients treated developing stable disease compared to 37% in controls ($p=0.0079$). A similar study[The CLARINET study](Controlled study of Lanreotide antiproliferative response in NETS) is being carried out in patients with PETs using Lanreotide autogel[36,37]. In various nonrandomized studies reporting the effects of either somatostatin analogues or interferon (principally alpha-interferon) tumoricidal responses with decrease in tumor size are rare ($<10\%$), however tumoristatic responses with a stabilization of tumor size are frequent (40–80%[7,36,37,45,152,154]. In some cases the tumoristatic effect is reported to be longstanding[102,154,155]. Whether this tumor-stabilizing effect will result in enhanced survival in patients with advanced PETs remains unproven at present. Long-term somatostatin treatment is generally well-tolerated with few patients stopping treatment because of side-effects, although potentially important side-effects could be a problem in some patients, including development of glucose intolerance/diabetes, steatorrhea (usually mild) and cholelithiasis (10–80% develop gallbladder sludge, 1%-symptomatic)[37,152]. With interferon, side-effects are more frequent with 80–97% developing a flu-like syndrome, however in most these improve with continued treatment[152]. More serious side-effect can develop including bone-marrow toxicity, hepatotoxicity, hyperlipidemia, autoimmune disorders and rarely CNS side-effects[7,37,152]. At present the exact role or sequence for use in patients with advanced PETs for somatostatin or interferon is unclear[37]. In the recent ENET guidelines it is concluded that in patients with advanced PETs with low proliferative rates (G1) that are slowly progressive, somatostatin analogues or if the tumor is somatostatin receptor negative, interferon treatment should be considered[36,37].

6D. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: liver-directed therapies

Treatments involving pharmacotherapy specifically directed at metastatic disease in the liver in patients with advanced PETs include: embolization, chemoembolization, radio-embolization or selected internal radiation therapy (SIRT) and are frequently used when diffuse, symptomatic or progressive metastatic disease is present which can not be treated surgically or by radiofrequency ablation[7,36,37,148,156–158]. Because the normal liver derives most of its blood supply from the portal vein, whereas PET liver metastases derive 70–80% of their blood supply from the hepatic artery, occlusion of hepatic arterial radicals affects tumoral deposits much more than normal liver[7,36,37,148,156–158].

Embolization is performed either alone or frequently with administration of various chemotherapeutic agents (most commonly used include: doxorubicin, 5-fluorouracil, cisplatin, mitomycin C, streptozotocin)[7,36,37,148,156–158]. In various studies 50–100% of patients have a symptomatic response to embolization/chemoembolization and 25–85% an objective tumor response with a mean duration of 6–45 months[7,36,37,148,156–158]. Both embolization and chemoembolization can be associated with serious side-effects with a complication rate of 10–80% including: a post-embolization syndrome of abdominal pain, fever and nausea/vomiting, as well as rarely, liver abscesses, gallbladder necrosis, hepatic and renal failure[7,36,37,148,156–158]. The mortality rate is $<6\%$. In both the recent NANTES[78] and ENETs[36] treatment guidelines, it was concluded that either

embolization/chemoembolization should be considered for palliative treatment in patients with hepatic-predominant metastatic NETs that is not surgically resectable, especially if symptomatic.

Radio-embolization or selected internal radiation therapy (SIRT) with ^{90}Y trium (^{90}Y) microspheres is a newer therapy with relatively few patients systematically studied and followed long-term, resulting in the recommendation in the 2012 ENETS treatment guidelines that it be still considered investigational [36,37,159–161]. Two types of microspheres are currently used: ^{90}Y resin microspheres (SIR-spheres, Sirtex Medical, Inc, Australia) with a 20–60 μm diameter and approximately 50Bq/sphere and glass microspheres (TheraSpheres, Nordion (Canada) with a 20-to 30 μm diameter with a radioactive content to 2500 Bq/sphere [36,37,159–161]. The mean overall objective tumor response rate from 12 studies with different types of unresectable metastatic NETs was 55% and stable disease was seen in 32% [37,161]. In general the side-effects are reported to be less than seen with embolization or chemoembolization with grade 2 or 3 side-effects including constitutional side-effects (fever, fatigue, weight loss) in 43% and 1% respectively, gastrointestinal side-effects (nausea, vomiting, pain) in 25 and 5% and radiation induced liver disease in >1% [37,159].

6E. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: Peptide radioreceptor therapy (PRRT)

As discussed above a high percentage (>90%) of well differentiated PETs including gastrinomas overexpress or ectopically express at least one of the five types of somostatin receptors (sst1–5) which can be targeted to deliver cytotoxic agents to the tumor [7,37,48,162]. To accomplish this, a number of different synthetic agonist analogues of somatostatin have been coupled to different cytotoxic radiochemical (primarily ^{111}In dium, ^{90}Y trium, ^{177}Lu tetium) using various chelators (primarily DTPA, DOTA) [7,37,48,162,163]. The most commonly used combinations are ^{90}Y -[DOTA 0 , Tyr 3]octreotide/octreotate, ^{90}Y -[DOTA]lanreotide or ^{177}Lu [DOTA 0 , Tyr 3]octreotate [7,37,48,162]. Of 10 studies (400 patients-malignant NETs) reporting results with ^{90}Y -labeled somostatin analogues [37] and one study with ^{177}Lu [DOTA 0 , Tyr 3]octreotate (510 patients), complete tumor responses were seen in 0–6% and 2%, respectively; partial/minor tumor regression in 7–37% and 43%; and tumor stabilization in 42–86% and 35%, respectively [37,162]. With ^{177}Lu [DOTA 0 , Tyr 3]octreotate [162] the mean duration of the objective response was not reached (>48 months). In a recent study specifically in patients with metastatic gastrinomas (11 cases) [163] with PRRT treatment with either ^{90}Y - or ^{177}Lu -somatostatin analogues, 9% showed a complete response, 45% a partial response and 45% tumor stabilization. Most side-effects with PRRT in the various studies were mild and with ^{177}Lu [DOTA 0 , Tyr 3]octreotate [162] mild symptoms (pain, vomiting, nausea) occurred in 30%. More severe side-effects included hematological toxicity (15% transient, 0.8% developed a myelodysplastic disorder) and liver toxicity (0.6%). Renal toxicity was seen primarily in patients receiving ^{90}Y -somatostatin analogues and this side-effect could be limited by co-administering an amino acid solution with treatment [7,37,48,162]. Although PRRT from these different reports appears to hold much promise, there are not controlled studies and only at present is a prospective study underway in patients with advanced NETs. The initial study which will start early next year (2013) will also include centers in the US but will be restricted to patients with metastatic ileal carcinoid disease. Therefore, at present in both the NANETS [78] and ENETS [36] guidelines for treatment of advanced NETs/PETs, PRRT is listed as an experimental/investigational treatment.

6F. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: Targeted medical therapy (mTor inhibitors (everolimus); tyrosine kinase inhibitors (sunitinib))

6F.1. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: Targeted medical therapy with mTor inhibitors (everolimus)—

Numerous experimental, molecular, clinical and pathological studies have provided evidence that mTOR serine-threonine kinase, plays an important role in regulation of the growth of NETs and particularly in PETs[9,37,37,42,164–166]. Everolimus[RAD001, Affinitor, Novartis AG, Basel, Switzerland] is an orally active mTOR inhibitor reported to have anti-growth effects on PETs in a number of studies[37,39,42,165]. Recently, the results of a double-blind, placebo-controlled, trial[RADIANT-3] of everolimus (10 mg/day) in 410 patients with advanced, progressive PETs has been reported[165]. In this study everolimus demonstrated a significant extension of progressive-free survival (11 vs 4.6 months, $p<0.0001$) and an increase by a factor of almost 4-fold the proportion of patients with progressive-free survival at 18 months of followup[165]. Overall survival between placebo/everolimus-treated groups did not differ; however, due to crossover from placebo to everolimus at the end of the study, the ability to calculate this was limited[42,165]. In the RADIANT-3 study everolimus treatment was associated with side-effects in some patients causing a two-fold overall increase in side-effects with most being grade 1 or 2, however grade 3 or 4 adverse events did occur. The most serious grade 3/4 events were: diarrhea, stomatitis, hyperglycemia and hematological (occurring in 3–7%)[165]. These side-effects could generally be managed by dose-reduction. Subsequently, in the US and Europe everolimus was approved for use in patients with unresectable, metastatic, well-differentiated PETs.

6F.1. Pharmacotherapy and treatment of advanced disease in patients with gastrinomas: Targeted medical therapy with tyrosine kinase inhibitors (sunitinib)—

Numerous studies demonstrate that PETs as well as other NETs, frequently possess tyrosine kinase receptors, including those of the epidermal growth factor family, insulin-like growth factor, hepatocyte growth factor[c-Met], platelet-derived-growth factor[PDGFR], stem cell factor[c-KIT], vascular-endothelial growth factors[VEGFR] and a number of others and that their activation can effect cell growth[7,37,166–168].

A number of small molecule inhibitors of these various tyrosine kinases activation have been developed, show antigrowth effects in PETs/NETs and are now undergoing studies in patients with advanced PETs/NETs[37,38,166–168]. At present the best studied and only one approved for use in patients with advanced, well-differentiated PETs is Sunitinib(Sutent, Pfizer, New York)[37,42,167,169]. Sunitinib is an orally active inhibitor of the tyrosine kinase activity of PDGFRs, VEGFR-1, VEGFR-2, c-KIT and FLT-3[167,169] PETs and has been shown to have anti-growth effects in patients with advanced PETs in an international, double-blind, randomized study[169]. In that study[169] 171 patients with progressive, advanced PETs were treated with sunitinib(37.5 mg/day) or placebo. Sunitinib treatment caused a doubling in the progression-free survival rate (11.4 vs 5.5 months, $p<0.001$), an increase in objective tumor response (9 vs 0%, $p=0.007$) and an increase in overall survival[169]. Sunitinib treatment was associated with a three-fold increase in side-effects of which most were grade 1 or 2. However some grade 3 or 4 adverse side-effects developed, with the most common being neutropenia (12%) and hypertension (9.6%) which could often be managed by dose-reduction[169]. Despite these side-effects there was no difference in a quality of life-index in the two groups of patients[169]. Subsequently, in the US and Europe sunitinib was approved for use in patients with unresectable, metastatic, well-differentiated PETs.

7. Pharmacotherapy of patients with gastrinomas-Conclusions

Since its original description, pharmacotherapy has played an increasing role in the management of patients with ZES, with the result that ZES has progressed from entirely a surgical disorder, to a disorder in which pharmacotherapy plays a role in all management aspects.

8. Pharmacotherapy of patients with gastrinomas-Expert Opinion

Pharmacotherapy, in one form or the other, is involved in all stages of the management of patients with ZES. It is involved in both a positive manner in many aspects of the management of ZES (control of hormonal hypersecretion, tumor localization studies, medical/other anti-tumor treatments) and in the case of the diagnosis of ZES, in a negative manner. The negative effect occurs because of the widespread use of PPIs in patients with various gastrointestinal complaints and even their increased over-the-counter use which can both complicate and delay the diagnosis of ZES. It complicates the diagnosis because PPIs can increase fasting gastrin levels, frequently in ranges that overlap with that seen in most ZES patients. Although an attempt can be made to decrease the PPI dose to achieve an acidic pH<2 while still taking a low dose of PPI, studies suggest in most patients the PPIs will have to be stopped to establish the diagnosis. This is time consuming because of the PPI's long duration-of-action and in a patient with ZES can be hazardous if not properly performed. The PPI's delay the diagnosis because, in contrast to histamine H₂-receptor antagonists, they control symptoms in most ZES patients with conventional doses and thus obscure the diagnosis. Pharmacotherapy has had a profoundly beneficial effect on allowing acid hypersecretion to be controlled medically in almost every patient with ZES as well as allowing effective treatments of other hormonal hypersecretory states that may develop. Pharmacotherapy has greatly enhanced the ability to localize gastrinomas and their extent by the use of various contrast agents with cross sectional imaging (CT, MRI) and angiography; the use of stimulants for hormonal gradient localization, and recently the use of radiolabeled somatostatin analogues for localization utilizing the ectopic, overexpression of somatostatin receptors by most gastrinomas. Lastly, pharmacotherapy is playing an increasing role in the treatment of patients with advanced, metastatic disease both in the form of different chemotherapy regimens, also with liver-directed therapies, biotherapy with somatostatin analogues or interferon, peptide radioreceptor therapy and most recently with effective molecular targeted therapies with the mTOR inhibitor, everolimus or the tyrosine kinase inhibitor, sunitinib. Many of these therapies are not specific to gastrinomas but also used in similar or related forms in the treatment of other PETs and NETS.

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Statements for highlight box

- Pharmacotherapy of Zollinger-Ellison syndrome (ZES) includes all aspects of management including medical control of acid hypersecretion, diagnosis, localization and treatment directed at the gastrinoma.
- Widespread use of PPIs for many GI complaints is making the diagnosis of ZES more difficult and is delaying the diagnosis
- The best method to diagnose ZES is controversial and this controversy is discussed in detail
- Certain aspects of ZES require modifications of standard antisecretory treatment and are discussed (pregnancy, parenteral therapy, complicated disease)
- Patients with advanced disease require treatments directed against the gastrinoma, a number of which are recently shown effective or promising including new chemotherapy regimens, molecular targeted therapies, biotherapies, and peptide-radioreceptor therapy
- Because of widespread use of pharmacotherapy in all aspects of management of ZES it has progressed from an entirely surgical disease to medical therapy playing an increasing major role.