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Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system

K. Öberg[1]*, L. Kvols[2], M. Caplin[3], G. Delle Fave[4], W. de Herder[5], G. Rindi[6], P. Ruszniewski[7], E. A. Woltering[8] & B. Wiedenmann[9]

[1]Department of Endocrine Oncology, University Hospital, Uppsala, Sweden; [2]University of South Florida, Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [3]Center for Gastroenterology, Royal Free Hospital, London, UK; [4]II School of Medicine, Ospedale Sant, Andrea, Università degli Studi di Roma 'La Sapienza', Rome, Italy; [5]Department of Internal Medicine, Section of Endocrinology, Erasmus Medical Center, Rotterdam, the Netherlands; [6]Departimento di Patologica e Medicina di Laboratorio, Sezione di Anatomica, Patologica, Universita degli Studi, Panua, Italy; [7]Hospital Beaujon, Service de Gastroenterologie, Clichy, France; [8]Lousiana University, Health Service Center, New Orleans, LA, USA; [9]Medizinische Klinik M.S., Head of Department, Hepatologie und Gastroenterologie, Berlin, Germany

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This consensus report gives a detailed description of the use of somatostatin analogs in the management of neuroendocrine tumors of the gastroenteropancreatic system. As background information we have outlined critical aspects of the pathology, the use of tumor markers, a definition of functional and non-functional digestive neuroendocrine tumors, different imaging modalities, surgical considerations, liver embolization and the use of cytotoxic drugs as well as interferon. Included in the report is an overview of somatostatin, somatostatin analogs and its receptor expression in different neuroendocrine tumors. It will also define the binding affinities of different somatostatin analogs to the five different subtypes of somatostatin receptor. We compare the efficacy of octreotide and lanreotide in reducing diarrhea and flushing. Side-effects are described and we provide practical information on somatostatin analog treatment.

Key words: gastroenteropancreatic system, lanreotide, neuroendocrine tumors, octreotide, somatostatin, somatostatin analogs, tumor markers, imaging

Introduction

The purpose of this article is to offer guidance to the practising physician on the clinical use of somatostatin analogs in patients with neuroendocrine tumors (NETs) of the gastroenteropancreatic (GEP) system. Both evidence-based medical data as well as prospective, randomized multicenter trials for the treatment of neuroendocrine tumors are very limited. Therefore, many of the recommendations made in this paper are based upon the collective experience of the authors. In addition to an in-depth discussion of somatostatin analog therapy in NET patients, descriptions of the critical aspects of tumor histology and various syndromes, tumor markers and imaging modalities are provided. Debulking of these tumors by surgical resection, locoregional ablation and embolic therapy with or without chemotherapy is discussed briefly. Numerous cytotoxic drugs as well as interferon-alpha have been studied in NET, mainly in single-center studies. However, few have been studied in a prospective fashion and are therefore not discussed in detail in this review.

**Correspondence to*: Dr K. Öberg, Department of Endocrine Oncology, University Hospital , SE-751 85 Uppsala, Sweden. Tel: +46-18-611-49-17; Fax: +46-18-50-72-68; E-mail: kjell.oberg@medsci.uu.se

Critical aspects of the pathology report

An adequate biopsy should be obtained with enough tissue to define tumor features and the biopsy should be repeated if the clinical course changes. A pathology report of practical use for the clinician should distinguish between well differentiated and poorly differentiated neoplasms [1, 2], and distinguish between well differentiated endocrine tumors (benign lesions), tumors of uncertain behavior and carcinoma.

To do this, several parameters should be assessed, including tumor size, invasion of nearby tissue or wall, invasion beyond the submucosa, angioinvasion, perineural space invasion, solid, organoid structure, presence of necrosis, more than two mitoses per high power field, Ki67 index >2%, loss of chromogranin A (CgA) immunoreactivity, argyrophilia or hormone expression.

Critical aspects of tumor markers

Chromogranins are co-released with the peptide hormones and amines present in secretory granules. Since CgA is stored in the majority of well differentiated NETs, its release into the circulation can be used as a 'marker' of the secretory activity of various tumors. CgA might also be a valid marker for 'non-functioning

NETs', which lack other suitable tumor markers. Analysis of CgA may be valuable in undifferentiated, CgA-positive NETs.

Several radio-immunoassay procedures for analyzing CgA have been developed in recent years and some assays are also commercially available. CgA is a very stable molecule and no special precautions are needed to store the serum or plasma. The levels of CgA are significantly elevated in most types of NETs, but particularly high levels are encountered in classical mid-gut NETs where levels of CgA may be increased 100- to 1000-fold.

Treatment with somatostatin analogs significantly reduces plasma CgA levels, especially in patients with classical mid-gut NETs. This change probably reflects an inhibition of both hormone synthesis and release from the tumor cells rather than a reduction in tumor mass. Therefore, changes in plasma CgA concentrations should be interpreted with care. In cases of progressive disease during treatment with somatostatin analogs, increased plasma levels of CgA may reflect a loss of secretory control and/or tumor growth. Interestingly, in some cases of tumor progression, CgA levels start to increase before changes in tumor size can be detected using computerized tomography (CT) or magnetic resonance imaging (MRI) [3]. Serotonin (5-HT) is an important marker for mid-gut NETs, which appears to be co-stored with CgA in secretory granules in NET cells and released upon stimulation. In contrast to its metabolite, urinary 5-hydroxy indole acetic acid (5-HIAA), determination of plasma levels of 5-HT is not useful in clinical practice.

In patients with pancreatic NETs, measurement of peptide levels is also critical. In cases where unusual symptoms are present or a multiple endocrine neoplasia (MEN) syndrome is suspected, a panel of peptide levels may be helpful. Clearly, if MEN syndromes are suspected these peptide level measurements should include simultaneous measurement of PTH, if the calcium is elevated and pituitary hormones or amines secreted by the adrenals. Suitable assay kits are commercially available or can be obtained from research laboratories.

Definitions of functional and non-functional digestive NETs

The terms 'functional/functioning' are used to denote the clinical manifestations of certain syndromes related to tumors that hypersecrete hormones (neuropeptides and biogenic amines) at supraphysiological levels. Accordingly, these neoplasms are named according to the hypersecreted hormone (e.g. insulinoma, gastrinoma, etc.). The clinical symptoms associated with functioning tumors frequently lead to their diagnosis at an early stage while the tumor is still small and resectable. Conversely, since elevated levels of pancreatic polypeptide or other peptides are not associated with a hypersecretion-related clinical syndrome, tumors that do not evoke symptomatic responses are therefore termed 'non-functional'. In such tumors, which represent about one-third to one-half of all NETs, no specific syndrome is present and symptoms are only related to the 'mass effect' caused by tumor growth or are just an occasional finding, and they are often first diagnosed only when they have already metastasized.

Which markers should be used in the clinic?

Serum or plasma CgA should be analyzed and correlated with a relevant marker for the syndrome, e.g. 5-HIAA (carcinoid syndrome), gastrin (gastrinoma), etc. Non-functioning tumors can be diagnosed biochemically using plasma CgA plus additional markers such as pancreatic polypeptide (PP) and human chorionic gonadotrophin alpha subunit (HCGα).

Both CgA and 5-HIAA are important markers for diagnosing mid-gut NETs.

Imaging modalities commonly used in NETs

Good quality imaging is required to determine the primary site of the tumor and the extent of metastatic disease. This is crucial not only for planning surgery but also to follow progression of the tumor and the response to therapy. The most evidence in assessing imaging is available for classical mid-gut NETs, gastrinomas and insulinomas [4–12]. There is little difference in sensitivity between CT and MRI, although the former is probably superior for localizing the primary tumor and thoracic lesions, whereas the latter may show benefit in characterizing liver lesions. Endoscopic ultrasound in experienced hands is probably the most sensitive technique for detecting pancreatic NETs, and permits fine needle aspiration of a lesion [13–16]. The most sensitive imaging modality for metastatic disease is somatostatin receptor scintigraphy (SRS; OctreoScan®), except for metastatic insulinomas, of which only 50% express type 2 somatostatin receptors (sst_2). Positron emission tomography (PET) may become a valuable tool in the detection of small NETs, but it is in the early stages of development for this group of patients. For mid-gut NETs, the serotonin precursor 5-hydroxytryptophan labeled with ^{11}C has a very high sensitivity. For the pancreatic NETs, other agents are being assessed, including L-DOPA and ^{18}fluoro-deoxyglucose (FDG)-PET [17, 18]. In patients with bony metastases, the isotope bone scan is still the gold standard [19, 20].

Surgical considerations

Surgery remains a mainstay in the treatment of NETs. Surgical approaches fall into three categories: (i) adequate resection with curative or palliative intent for primary and regional lesions; (ii) surgical resection of regional or distant metastatic disease with a cytoreductive intent; and (iii) resection of disease for palliation of symptoms without cytoreductive intent.

Cytoreductive surgery, which includes tumor resection, radiofrequency ablation and cryotherapy, is designed to either remove or destroy tumor in an effort to control clinical symptoms and enhance patient survival. Whenever possible, gross tumors are removed from the primary site and regional lymphatics. For islet cell tumors such as insulinomas, this may require little more than simple enucleation, though for clearly malignant tumors, more aggressive surgical approaches including pancreatoduodenectomy may be warranted. Many patients with NETs receiving cytoreductive procedures on the liver will have been treated with somatostatin analogs, or will be future candidates for long-term somatostatin analog therapy. Since a common side-effect of

Table 1. Binding affinities of somatostatin analogs to the five human somatostatin receptor subtypes (hssts) [39]

Compound	$hsst_1$	$hsst_2$	$hsst_3$	$hsst_4$	$hsst_5$
Somatostatin 14	0.93 ± 0.12	0.15 ± 0.02	0.56 ± 0.17	1.5 ± 0.4	0.29 ± 0.04
Lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5
Octreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
SOM 230 [27]	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>100	0.16 ± 0.01

IC_{50} values are expressed in nanomoles (mean ± standard error of the mean).

somatostatin analog therapy is cholelithiasis, whenever a surgical procedure is planned that requires abdominal exploration, a cholecystectomy should be performed in anticipation of somatostatin or embolic therapy.

The goal of cytoreductive surgery is to improve symptoms by controlling peptide/amine excess, to improve the quality of life and extend survival. Partial hepatectomy for metastatic gastrointestinal or pancreatic NETs has proved to be an effective way of controlling symptoms. Recently, a meta-analysis summarizing 26 years of medical literature on cytoreductive procedures on NETs was published [21]. The mean 5-year survival rates in midgut NET patients undergoing cytoreduction and in patients with metastatic islet cell tumors following partial hepatectomy were well over 50%. Overall, 5-year survival of patients following orthotopic liver transplantation for metastatic NET was ~50% and median survival was 5.1 years. Survival following orthotopic liver transplantation for NETs or conventional cancers was also high.

Hepatic arterial chemoembolization

Locoregional treatment (such as ligation or embolization of the hepatic artery and intra-arterial hepatic chemotherapy) has allowed transient control of hepatic tumor growth in patients with metastatic NETs. The combination of cytotoxic chemotherapy and local ischemia, i.e. chemoembolization, has been evaluated in several studies.

Symptomatic responses were obtained in most patients, while tumor shrinkage was observed in about half of the patients with progressive disease before chemoembolization.

The use of interferon treatment in NETs

Alpha interferon (α-IFN) has been used for >20 years in the treatment of mid-gut NETs and is registered in most European countries.

Symptomatic and biochemical responses are seen in 50% of patients, with significant tumor reduction in 10–15%. The most severe side-effects are flu-like symptoms and autoimmune phenomena (e.g. thyroiditis).

The role of chemotherapy in patients with NETs

Currently, in contrast to pancreatic NETs, neither single-agent nor combination chemotherapy for metastatic gastrointestinal NETs have been shown to have major activity. Responses, when they do occur, are usually short-lived so the identification of new agents continues to be a challenge to clinicians [22].

Comments on the roles of chemotherapy in different NETs

Although most NET cells are endodermally derived and possess similar, unique morphology, there appear to be considerable differences in chemosensitivity in relation to primary tumor location. There has been progress in the treatment of some of these rare tumors (e.g. pancreatic NETs), while in others we are continuing to use therapies that have remained unchanged for many years. Exciting developments in the manipulation of the cellular regulation of endocrine secretion may enable us to retard the growth of the malignant cells without the toxicity of chemotherapy. Large-scale cooperative studies are urgently required to evaluate new therapeutic modalities fully. Patients with these rare neoplasms should be entered into prospective clinical trials whenever possible.

Therapy with somatostatin analogs

Native somatostatin consists of two cyclic peptides of 14 and 28 amino acids, respectively. The peptides play an inhibitory role in the regulation of several organ systems and tissues [23]. For example, somatostatin inhibits a variety of physiological functions in the gastrointestinal tract, including gastrointestinal motility and the secretion of pancreatic and intestinal hormones such as insulin, glucagon, secretin and vasoactive intestinal polypeptide (VIP).

Since native somatostatin has only limited clinical usefulness due to the need for intravenous administration, the short duration of action (half-life <3 min) and the post-infusion rebound hypersecretion of hormones [24, 25], synthetic somatostatin analogs were developed. Octreotide was the first such analog. Its elimination half-life after subcutaneous administration is 2 h and rebound hypersecretion of hormones does not occur [23]. Somatostatin and its analogs exert their effects through interaction with somatostatin receptor (sst) subtypes 1–5 (sst_1 to sst_5). Native somatostatin binds with high affinity to all somatostatin subtypes, whereas octreotide binds with a high affinity to sst_2 and with a somewhat lower affinity to the sst_3 and sst_5 receptors [26]. Other cyclic analogs with very similar affinity and activity profiles, such as lanreotide, have been developed (Table 1) [23].

Table 2. Expression of somatostatin receptors[a] in neuroendocrine gastroenteropancreatic tumors (%)

	sst_1	sst_2	sst_3	sst_4	sst_5
Endocrine pancreatic tumors					
All tumors	68	86	46	93	57
Insulinoma	33	100[b]	33	100	67
Gastrinoma	33	50	17	83	50
Glucagonoma	67	100	67	67	67
VIPoma	100	100	100	100	100
Non-functioning	80	100	40	100	60
Mid-gut neuroendocrine tumors	80	95	65	35	75

VIP, vasoactive intestinal polypeptide.
[a]Using receptor subtype antibodies [32].
[b]Malignant insulinoma.

Somatostatin analogs can control hypersecretion in NETs that express somatostatin receptors. In sst_2- or sst_5-positive tumors, clinical symptoms related to hypersecretion can be controlled by the long-term administration of one of the currently available somatostatin analogs [23, 26], as shown in Table 2. In addition, these agents may also exert some anti-proliferative actions [28]. Endocrine pancreatic and digestive tract tumors can express multiple sst subtypes, but sst_2 predominance is found in >80% of these tumors [29–31].

Octreotide has been registered in most countries for the control of hormonal symptoms in patients with gastrointestinal and pancreatic NETs, as well as in patients with acromegaly. Somatostatin analogs can be administered by multiple subcutaneous (s.c.) injections or by continuous s.c. infusion as well as by the intravenous (i.v.) route, either as a single injection or as a continuous infusion over many hours or days. The slow-release intramuscular (i.m.) formulation of octreotide (Sandostatin LAR®) is usually administered once every 4 weeks, and that of lanreotide (Somatuline® LA) is administered once every 2 weeks. Comparative data on these two agents are shown in Table 3.

A new slow-release depot preparation of lanreotide, Somatuline Autogel®, has been introduced in several European countries. It is administered by deep s.c. injection once every 4 weeks. Published data on this new preparation in NET patients are lacking at present, and it is therefore not discussed in more detail in this paper. Other drugs with affinities to other somatostatin receptor subtypes have been developed recently and are currently undergoing phase I and II testing [34].

Tumors and metastases that bear sst_2 or sst_5 can be visualized *in vivo* after injection of radiolabeled octapeptide analogs such as ^{111}In-pentetreotide [OctreoScan® ([^{111}In-DTPA0]octreotide)] and [^{111}In-DOTA0]lanreotide [35, 36]. Radiolabeled octapeptide analogs such as ^{111}In-pentetreotide [^{90}Y-DOTA0,Tyr3]octreotide (OctreoTher®), [^{177}Lu-DOTA0Tyr3]octreotate, [^{111}In-DOTA0]lanreotide and [^{90}Y-DOTA0]lanreotide, can also be used for radiotherapy of sst_2- and sst_5-positive advanced or metastatic endocrine tumors [36–40].

Practical aspects of octreotide therapy

The practical aspects of using octreotide, the most widely used somatostatin analog and the analog with which the authors have the most clinical experience, are addressed in this section. Guidelines are provided on which patients should be treated, when treatment should be started, how to use the immediate release (IR) and the long-acting release (LAR) formulations, pre- and peri-operative use, and what to do when symptoms do not respond or begin to escape from control.

Patients benefiting from treatment with octreotide include those with functional NETs of fore- and mid-gut origin. Glucagonomas, VIPomas and to a lesser extent gastrinomas and metastatic insulinomas are examples of functioning pancreatic endocrine tumors amenable to treatment with octreotide. Selection of patients is based on a positive OctreoScan® or, less frequently, a suppression test where a >50% decrease in peptide/amine levels is seen 1–2 h after administration of 100 μg octreotide s.c. Other syndromes where octreotide may provide benefit include ectopic adrenocorticotropic hormone (ACTH) secretion with Cushing's syndrome, oncogenic osteomalacia, and hypercalcemia due to the secretion of ectopic parathyroid hormone-related peptide.

A more controversial area concerns the treatment of patients with non-functioning endocrine tumors of the GEP system.

Common adverse effects of treatment with somatostatin analogs include nausea, abdominal cramps, loose stools, mild steatorrhea (presumably resulting from transient inhibition of pancreatic exocrine secretion and malabsorption of fat) and flatulence. These symptoms start within hours of the first s.c. injection, are dose-dependent, and usually subside spontaneously within the first few

Table 3. Comparative features of octreotide and lanreotide [55]

	Octreotide	Lanreotide
Reduction of diarrhea [33]	50%	45%
Reduction in flushing [33]	68%	54%
Most common adverse events	Gastrointestinal disorders, biliary disorders, injection site pain	Gastrointestinal disorders, biliary disorders, injection site pain
Availability of short-acting formulation	Yes	No
Frequency of administration	Every 4 weeks	Every 2–4 weeks

weeks of treatment. There may be local pain and erythema at the injection site. Impaired glucose tolerance or even overt diabetes mellitus (resulting from transient inhibition of insulin secretion) have also been observed during therapy with somatostatin analogs [23]. A very rare side-effect is gastric atony [41]. Because of these adverse events, administration of the IR formulation is recommended before the administration of the intramuscular depot formulation.

The risk of developing gallstones and/or gallbladder sludge in patients with metastatic gut NETs or malignant islet cell tumors undergoing therapy with somatostatin analogs approaches 50% [42]. The prevalence of somatostatin analogue-induced gallstones in acromegalic patients varies geographically and may be influenced by dietary, environmental or racial factors. The formation of gallstones during somatostatin analogue therapy probably involves inhibition of gallbladder contraction and emptying, inhibition of the secretion of cholecystokinin, and increased intestinal and biliary production of deoxycholic acid. It has been suggested that gallstone development in patients receiving somatostatin analogs for metastatic gastrointestinal or pancreatic NETs is dose-dependent. Despite the high incidence of new gallstones in patients receiving somatostatin analogs, only ~1% of patients develop acute symptoms requiring cholecystectomy.

In patients with metastatic gut NETs or malignant islet cell tumors undergoing somatostatin analogue therapy, cholecystectomy should be performed if the patient is undergoing surgery for bowel resection or cytoreductive surgery.

When should somatostatin analog treatment be started?

There are accepted as well as more controversial indications for beginning somatostatin analog therapy. The accepted indications for the use of a somatostatin analog include: patients with peptide-/amine-induced syndromes with clinical symptoms, and patients with progression of metastatic disease even without a syndrome. The peri-operative use of somatostatin analogs is critical in the prevention of 'carcinoid crisis'. More controversial indications include: use after debulking procedures such as surgical, radiofrequency ablation or embolization; adjuvant treatment with octreotide in patients who have no evidence of residual disease; and an asymptomatic patient at the time of diagnosis of metastatic disease.

How should octreotide be prescribed for optimal symptom control?

The optimum approach for using this drug is to initiate therapy in the form of s.c. injections of the IR formulation for 3–7 days to test for tolerability before giving the LAR formulation i.m. The s.c. injections should be continued for ~14 days after the LAR injection since therapeutic levels are not achieved until that time. It is important to emphasize to the patient that the IR octreotide should be used for breakthrough symptoms after the start of LAR treatment. The use of this as 'rescue' medication is vital to optimize control of the symptoms.

The initial dose of IR octreotide may range from 100 to 500 μg s.c., two to four times daily. A reasonable starting dose is 150 μg s.c. three times daily (t.i.d.). Some investigators prefer continuous s.c. infusion of octreotide by pump at a dose of 1000–2000 μg daily. The dose of IR octreotide may be escalated until maximum control of symptoms is achieved by doubling the dose at 3- or 4-day intervals.

The majority of patients will prefer the convenience of once monthly injections with the LAR formulation. Most new patients are initially treated with the 20 mg dose of LAR. There is little if any role for 10 mg LAR in NET patients. As a general rule, if the total IR dose is 200–600 μg/day, LAR 20 mg should be tried, and if total IR dose is 750–1500 μg/day, LAR 30 mg should be tried. The LAR doses range from 20 to 60 mg every 28 days.

Supplementary administration with the IR form of octreotide in patients escaping anti-secretory response is often required during long-term treatment with LAR. If it is necessary to give the patient rescue doses of IR octreotide three or four times per week, increase the LAR dose to 30 mg/4 weeks, or reduce the interval between administrations of the depot formulation (e.g. 20 mg every 3 weeks). Furthermore, the temporal occurrence of hypersecretion during the 4-week dosing interval should be considered. For example, if the rescue s.c. therapy is required during the week before the next injection of LAR, then a reduction of the dosing interval by 1 week is advisable. On the other hand, if the need for rescue medication occurs sporadically throughout the month then increasing the dose stepwise by 10 mg/month up to 60 mg/month should be tried. Doses of LAR >60 mg/month are rarely of added value. At this juncture one could consider resuming s.c. injection, switching to a continuous infusion pump or adding a new agent.

The duration of therapy with octreotide is usually lifelong unless unmanageable side-effects occur or there is a total loss of symptom control.

How should a patient on somatostatin analog therapy be followed?

A complete history and physical examination should be performed every 3 months. The patient should be examined using conventional imaging studies (CT/MRI or ultrasonography) every 6 months. Patients with progressive disease should be scanned before therapy and every 3 months until stability is seen for two consecutive scans.

Annual OctreoScans® are controversial, but they may be indicated when new symptoms appear. Biochemical parameters (tumor markers) are repeated every 3–6 months. For gastrointestinal NET patients, this includes CgA and a 24-h urine collection for determination of 5-HIAA. For pancreatic NETs, the predominant peptide should be measured every 3–6 months. It is of note that patients with non-functional gastrointestinal as well as pancreatic NET tumors may develop functional hormone secretion during tumor progression.

Responses to octreotide therapy are defined according to three categories: symptomatic, biochemical and objective (radiologic). Symptomatic responses are reductions in hypersecretion-related/hormonally mediated symptoms such as diarrhea or hypoglycemia, and in non-functional NETs they are reduction in tumor bulk-related symptoms such as upper abdominal pain, and improvement in quality of life or performance status. Biochemical responses are defined as a ≥50% decrease in tumor (serum/urine)

markers. The importance of biochemical responses is controversial, but an early and dramatic reduction in markers may portend a more durable response to octreotide [43]. Objective responses according to World Health Organization and RECIST (response evaluation criteria in solid tumors) criteria are rare with octreotide. However, in about one-third of the patients who show progressive disease before somatostatin analog therapy, stable disease is observed after initiation of treatment [44].

What is the role of SRS in the follow-up of patients with NETs?

In contrast to sectioning imaging procedures (e.g. CT, ultrasound and MRI), SRS may show early evidence, based on the whole body scan, of additional lesions not revealed by other procedures. SRS may also provide evidence of a local biological response versus an anatomical response, e.g. necrosis. Thus, the loss of the SRS signal in a given lesion as well as the detection of additional lesions in other organs missed using conventional imaging procedures may affect therapeutic management.

To obtain optimal SRS scans, treatment with octreotide should be interrupted in patients on chronic therapy. For patients treated with s.c. IR octreotide, treatment should be stopped for 24 h before the scan. It can be restarted 4–6 h after the OctreoScan® injection without interfering with the quality of the images. For patients treated with the LAR formulation, the scan should be performed just before next LAR administration. However, in patients with severe functional symptoms, data from several centers suggest that maintenance of somatostatin therapy does not influence SRS results.

What is the role of octreotide in patients receiving radiolabeled somatostatin therapy?

As with SRS, therapy with unlabeled octreotide should be stopped before the administration of radiolabeled somatostatin analogs. Theoretically, occupation of the binding sites for somatostatin prevents the receptor sites from being occupied when the radionuclide/peptide combination is administered. We recommend stopping the IR form of octreotide for 24 h before radiotherapy. For patients receiving the depot formulations of octreotide, treatment should be interrupted >2 months before radiotherapy. In this situation, the patient can switch to the IR formulation.

How should octreotide be administered during invasive procedures?

The use of octreotide before invasive procedures is important to prevent 'carcinoid crisis'. In patients in whom symptoms are well controlled by LAR 20/30 mg, a supplementary bolus dose of 250–500 μg octreotide should be given s.c. within 1–2 h before the procedure. For emergency surgery in therapy-naïve patients with functional NETs, a 500–1000 μg i.v. bolus of octreotide or 500 μg s.c. should be given 1–2 h before the procedure.

The recommended intra-operative use of octreotide for carcinoid crisis with hypotension is bolus i.v. doses of 500–1000 μg, with treatment repetition at 5-min intervals until control of symptoms is achieved. Alternatively, following an i.v. bolus dose, continuous i.v. infusion of octreotide at a dose of 50–200 μg/h may be given. In any patient who has required supplemental dosing during a procedure, the post-operative dose would be 50–200 μg/h for 24 h, followed by resumption of the preoperative treatment schedule.

Do patients with NETs develop drug resistance?

Resistance to octreotide in terms of symptom control and/or tumor growth can be defined in several ways: (i) primary absolute failure to achieve symptomatic and/or tumor growth control in spite of dose escalations; (ii) secondary failure of response to dose escalations after initial control of symptoms and/or tumor growth; and (iii) in spite of excellent symptom control of functional symptoms, an increase in tumor size or tumor markers. In the latter case, additional treatment options such as hepatic arterial chemoembolization or local thermal ablation of hepatic metastases may be considered. During these procedures octreotide therapy should be continued for symptom control. Also, the addition of interferon or even chemotherapy could be considered. Most importantly, consideration should be given to referring the patient for participation in experimental protocols.

The use of octreotide as therapy for paraneoplastic syndromes

In patients with the ectopic ACTH secretion and Cushing's syndrome, octreotide therapy can result in a reduction of ACTH levels in some cases [44, 45]. However, the unpredictable response as well as the generally incomplete normalization of ectopic ACTH overproduction in response to octreotide usually necessitates early (laparoscopic) bilateral adrenalectomy in these generally severely ill patients. Tumor-induced osteomalacia, also called oncogenic osteomalacia, is presumably caused by the paraneoplastic production of phosphatonins, which cause renal phosphate wasting [46]. As these tumors may express somatostatin sst_2 receptors, which probably interfere with phosphatonin release, this paraneoplastic syndrome may well respond to octreotide therapy [47, 48]. NETs producing parathyroid hormone-related peptide are usually undifferentiated and can express somatostatin sst_2 receptors. These rare tumors become clinically apparent with various degrees of hypocalcemia. In these selected cases a trial with octreotide treatment may improve the clinical and biochemical picture [49–51]. Similarly, in ectopic acromegaly caused by GHRH (growth hormone releasing hormone) production by NETs, octreotide treatment suppresses paraneoplastic GHRH secretion by the tumor as well as ectopic pituitary GH (growth hormone) hypersecretion, resulting in a (near-) normalization of pathologically elevated GH, GHRH and insulin-like growth factor I (IGF-I) [52–54].

Are there alternative treatments when octreotide therapy fails?

Occasionally a patient not tolerating octreotide may benefit from lanreotide [55]. Conversely, those patients who fail lanreotide therapy may benefit from a trial of octreotide.

Due to its potent anti-secretory actions, octreotide is one of the few oncologic drugs that is continued in the face of tumor progression. Furthermore, it may be used with other modalities without additional toxicity.

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