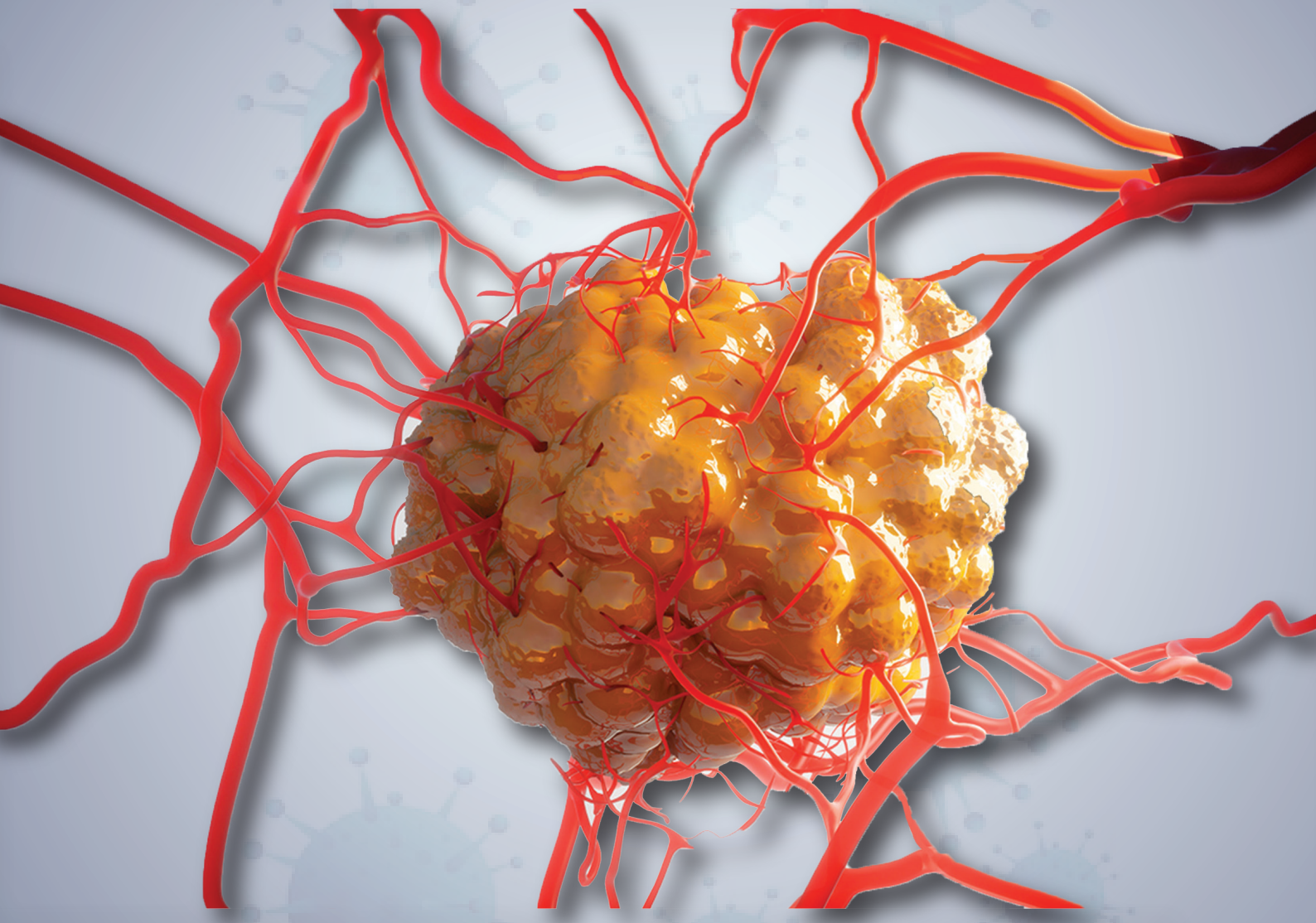
Module in The Area of **Medical Oncology**



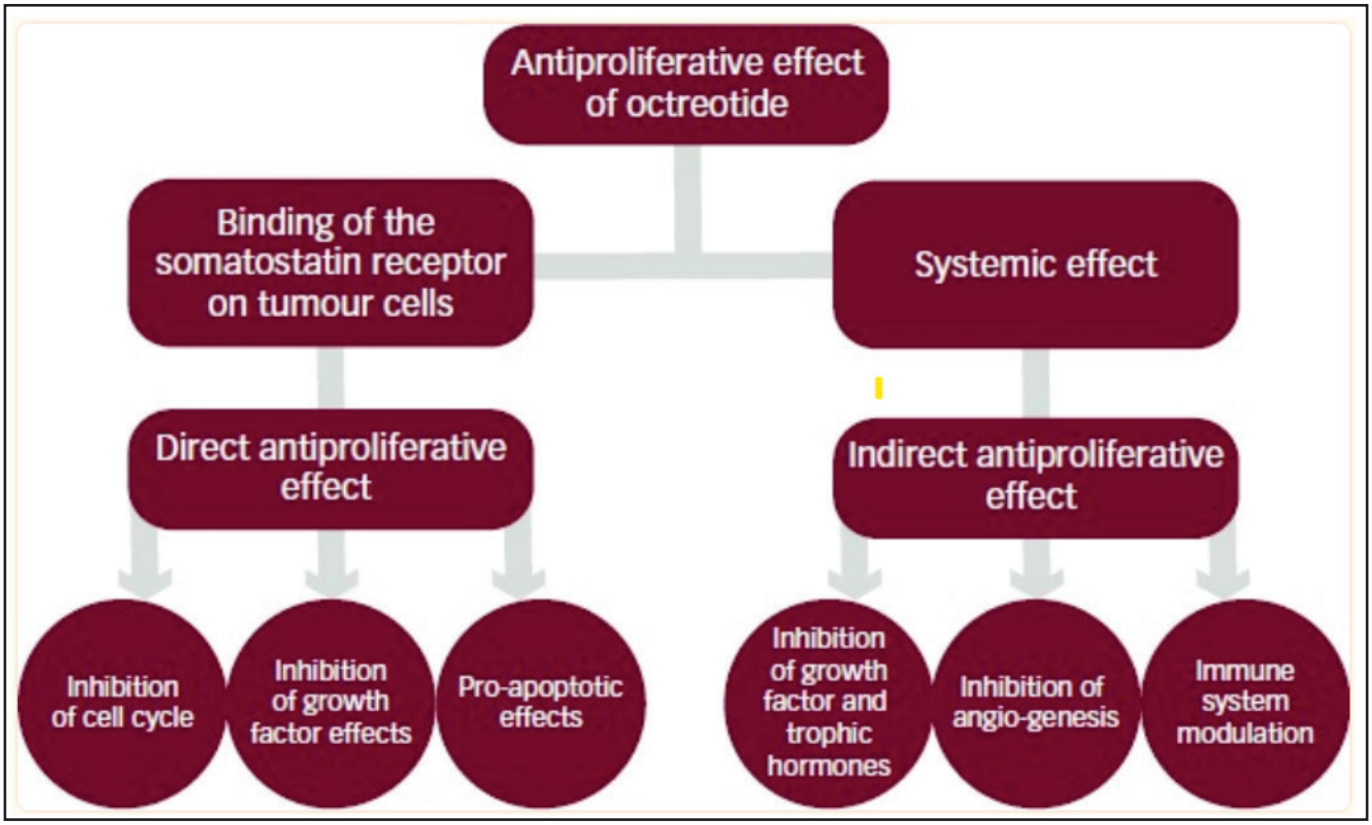
Module II

Role of Octreotide in Medical Oncology.

CONTENT

Introduction

Octreotide is a synthetic octapeptide SSA with more prolonged pharmacological actions than the endogenous hormone. Native somatostatin has a half-life of 2–3 minutes; octreotide has a half-life of 90–120 minutes when administered subcutaneously, and a pharmacodynamic action lasting up to 8–12 hours. Since octreotide resembles somatostatin in its physiological activities, it affects numerous pathways that may confer antiproliferative effects in NETs through inhibition of tumour angiogenesis and inhibition of secretion of growth factors. Direct mechanisms by which octreotide achieves and tumour regression include binding to somatostatin receptors sst2 sst5, which are found in high density on tumour cells, and thereby inhibiting hormone secretion from the tumour, inducing apoptosis and cell cycle arrest, mainly through the regulation of phosphotyrosine phosphatase (PTP) and mitogen-activated protein (MAP) kinase. Binding to sst2 and sst5 receptors, octreotide blocks the effects of growth factor receptor stimulation and results in increased production of the cell cycle inhibitor p27. Binding to sst2 receptors, SSAs affect the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway and SHP1 signalling and may overlap with pathways used by the mTOR inhibitor, everolimus. Indirect effects include inhibition of angiogenesis and the release of secretory factors required for tumour growth, as well as modulation of the immune system and inhibition of insulin-like growth factor 1 (IGF-1) secretion.*(Costa F,et al; Oberg K,et al; Kimura W,et al; Yao JC,,et al; Modlin IM,et al; Lal A,,et al; Bauer W,,et al; Florio T,et al; Susini C,et al; Chadha MK,et al; Theodoropoulou M,et al; Grozinsky-Glasberg S,et al)*



Octreotide is approved in the US and Europe for treatment of severe diarrhoea/flushing episodes associated with metastatic carcinoid tumours and profuse watery diarrhoea associated with vasoactive intestinal polypeptide (VIP)-secreting tumours .Octreotide is also approved in 42 countries for tumour control for advanced midgut NETs based on the Placebo-Controlled Prospective Randomized Study on the Antiproliferative Efficacy of Octreotide acetate LAR in Patients with Metastatic Neuroendocrine Midgut Tumours (PROMID) study. Additionally, treatment guidelines now recommend the use of octreotide as an antiproliferative agent in patients with functional and non-functional midgut NET,based on results from the randomised phase III PROMID trial.17 Pooled data from more than 14 trials including almost 400 patients revealed that 71 % of patients with GEP-NETs and carcinoid syndrome experience resolution or improvement of diarrhoea (range: 40–88 %) and flushing (range: 48–100 %) during treatment with octreotide. Octreotide can be used peri-operatively and may prevent carcinoid crisis, i.e. the immediate onset of debilitating and life-threatening symptoms that are associated with carcinoid syndrome.*(Costa F,et al)*

The development of the long-acting release (LAR) formulation of octreotide in 1997 (Sandostatin® LAR, Novartis) further improved the clinical utility of this drug. Octreotide acetate LAR (octreotide LAR) is a formulation in which octreotide acetate is encapsulated in microspheres of a slowly dissolving polymer, providing a predictable pharmacokinetic profile and steady-state kinetics when injected intramuscularly once every 28 days.23 Octreotide LAR retains the pharmacological characteristics of the previous subcutaneously (SC) administered formulation of octreotide, and reaches steady-state concentrations within three injections.24 A retrospective study compared survival in 145 patients with carcinoid syndrome who received octreotide LAR between 1996 and 2004 to 90 patients who received SC octreotide between 1986 and 1995. Patients who received treatment with octreotide LAR had a 66 % (range 46–82 %) lower risk of death than patients who had received SC octreotide ($p<0.0001$).
(Costa F,et al)

Octreotide in Neuroendorcine Tumors

Neuroendocrine tumours (NETs) is a collective term for a diverse range of neoplasms that arise from cells that originate in the endocrine and nervous systems and share common morphological and immunohistochemical features, including the presence of secretory granules. These tumours can secrete a variety of neuropeptides, which may or may not cause characteristic hormonal symptoms (functioning or non-functioning NETs). *(Costa F,et al)*

NETs have generally been considered rare; their incidence has been estimated at 2.5 to 5 per 100,000 people per year and prevalence of 35 per 100,0001 and may be higher if undiagnosed NETs are included. *(Costa F,et al)*

NETs that secrete peptides and neuroamines can cause recognisable clinical syndromes, including carcinoid syndrome.4 However, due to the indolent nature of NETs, many patients are asymptomatic in the early stages, or present with only vague symptoms such as abdominal pain.4 As a result, NETs are frequently metastatic at the time of diagnosis: liver metastases are observed in 40 % of patients who present with small intestinal and 60–70 % of patients with pNETS.3,5 Other factors influencing the presence of liver metastases include the primary tumour site, tumour stage, histological differentiation and proliferative activity (grading; G1–G3). Carcinoid syndrome is frequently associated with distant metastases, especially in the liver. The prognosis for NETs varies according to proliferative activity: median survival in distant metastatic disease was 33 months in patients with G1–G2 graded NETs, but only 5 months in patients with poorly differentiated carcinomas.3 The 5-year survival rate was 35 % in well to moderately differentiated (grade 1/2) NETs, but less than 5 % in poorly differentiated grade 3 NETs. *(Costa F,et al)*

The first-line treatment strategy for NETs is surgery, but this is rarely curative, as most patients present at advanced stages of disease.3,5 Other treatment options include cytoreduction, radiological intervention (by embolisation and radiofrequency ablation) and chemotherapy.4 Surgical debulking can reduce the extent of hormone production and relieve symptoms, but owing to the long disease course, palliative care is important. Somatostatin analogues (SSAS), including octreotide and lanreotide, were introduced to control symptoms that result from release of peptides and neuroamines. Octreotide is the most studied SSA.

Clinical Data Demonstrating the Antiproliferative Effect of Octreotide

There is a long history of evidence for the antiproliferative effects of octreotide. Evidence from preclinical cancer models showed that octreotide LAR had antitumour activity.In prospective studies, octreotide LAR has exhibited an antiproliferative effect in the following types of NET: entero-pancreatic, well-differentiated endocrine carcinomas,gastric carcinoid tumours,metastatic or locally advanced, well-differentiated NETs,progressive NETs of the pancreas and bronchial tract31 and advanced, progressive metastatic gastrinoma characterised by Zollinger-Ellison syndrome (ZES) and liver metastases. summarises clinical studies that have demonstrated the antiproliferative effect of short-and long-acting formulations of octreotide. .(Costa F,et al; Oberg K,et al; Kimura W,et al; Yao JC,,et al; Modlin IM,et al; Lal A,,et al; Bauer W,,et al; Florio T,et al; Susini C,et al; Chadha MK,et al; Theodoropoulou M,et al; Grozinsky-Glasberg S,et al)

Study Type	Regimen	Results
Phase II trial, n=34, patients with advanced functioning (n=21) and not functioning (n=13) carcinoid or islet cell NETs	Octreotide SC 250 µg TID	SD in 50 % of patients for median 5 months (range 2–27 months)
Phase II trial, n=103, metastatic GEP-NETs. 64 functioning and 39 non-functioning	Octreotide SC 200 µg TID	SD in 36.[5] % of patients for median 18 months (range 3 to >42 months)

Study Type	Regimen	Results
Phase II trial, n=58, patients with histological evidence of carcinoid or other NETs	Octreotide SC 500 µg TID (n=23) versus octreotide SC 1,000 µg TID (n=35)	SD in 47 % for at least 6 months and at least 1 year in 22 %; PR in 3 %
Prospective study, n=35, 18 functional, progressive metastatic NETs	Octreotide acetate LAR SC 100 µg three times daily (max 100 µg 3 times/day) or lanreotide 30 mg every 14 days (max 30 mg/10 days)	SD in 57 % for median 7 months. PR in 3 %
Phase II trial, n=32, progressive, metastatic, pNETs	Octreotide acetate LAR 30 mg/28 days (n=20) versus lanreotide SR 60 mg/28 days (n=11)	SD in 45.2 % of patients for 6–60 months
Prospective study, n=15, gastric carcinoid tumours type 1	Octreotide acetate LAR 20–30 mg/month (n=14) or lanreotide 90 mg/monthly (n=1)	At 1 year, 73 % observed complete disappearance of tumours; 20 % had a significant decrease in the number and size of tumour
Prospective study, n=15, advanced progressive metastatic gastrinoma characterised by Zollinger-Ellison syndrome and liver metastases	Octreotide acetate LAR 30 mg/28 days	At 3 months, SD in 47 %. Mean duration of response was 25.0±6.1 months (range 5.5–54.1 months)
Prospective phase IV study (n=21), well-differentiated, non-functioning advanced pNET	Octreotide acetate LAR 30 mg/28 days	SD in 35 %
Phase III study (n=19),	Octreotide acetate LAR 30	SD in 26 %, PR in 11 %

Study Type	Regimen	Results
progressive NETs of the pancreas and bronchial tract	mg/28 days versus chemotherapy (streptozotocin + 5-fluorouracil)	
Phase III study (PROMID), n=85, well-differentiated metastatic NETs of the midgut	Octreotide acetate LAR 30 mg/28 days versus placebo	At 6 months, SD in 66.7 % versus 37.2 % placebo; PR in 2 %
Phase III multinational, randomised, double blind trial RADIANT-2	Everolimus 10 mg/day + octreotide acetate LAR 30 mg/28 days versus placebo + octreotide acetate LAR 30 mg/28 days	SD 84 % versus 81 % in placebo; PR in 1

Octreotide may also be used in asymptomatic patients at the time of diagnosis of metastatic disease.19 There is evidence that the impact of octreotide extends beyond symptom relief. A single-institution retrospective study of 90 consecutive patients with advanced GEP-NETs who received octreotide for carcinoid syndrome, found that a much greater percentage of patients treated with octreotide achieved 5-year survival from diagnosis compared with historical controls (67 % versus 18 %, respectively).22 Subsequent analysis of the SEER database found that survival in patients with metastatic NETs increased from 19 months (1973 to 1987) to 39 months (1988 to 2004) following the introduction of octreotide . This increased survival was observed in patients with GEP-NETs and distant metastases; patients with localised and regional disease did not exhibit significantly extended survival time. A possible explanation for this improvement may be that not only does octreotide achieve control of the symptoms of carcinoid syndrome but also has a potential antiproliferative effect, which could alter the natural history of NETs. Potential lethal consequences associated with carcinoid crisis, such as severe flushing, diarrhoea, valvular heart disease and haemodynamic instability, are now rare occurrences. Complications due to tumour progression tend to occur later in the disease course

The most robust data have been provided by the phase III PROMID trial. In this study, newly diagnosed and treatment-naïve patients were randomised to placebo or octreotide LAR administered intramuscularly every 28 days for 18 months or until tumour progression or death. To avoid a heterogeneous patient population with GEP-NETs of different origin and biological behaviour, only patients with well-differentiated metastatic or locally inoperable midgut tumours were included.Midgut NETs represent the largest subgroup of NETs, and by targeting these patients, the PROMID study therefore involved the largest homogeneous NET patient population.

Enrolment criteria permitted patients to have either a functioning (patients that could tolerate symptoms with loperamide and clinical support) or non-functioning tumour: those with symptoms of carcinoid syndrome and increased urinary 5-hydroxyindole acetic acid (5-HIAA) were classified as having a functioning tumour. Hepatic tumour load (HL) was quantified by computed tomography (CT) or magnetic resonance imaging (MRI). *(Costa F,et al)*

Results from 85 patients showed that the median time to tumour progression (TTP) in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (hazard ratio [HR] = 0.34; 95 % confidence interval [CI] 0.20–0.59; p=0.000072). After 6 months of treatment, stable disease was observed in 66.7 % of patients in the octreotide LAR group and 37.2 % of patients in the placebo group. The HR for overall survival (OS) was 0.81 (95 % CI 0.30–2.18). Most patients in the PROMID study benefited from octreotide LAR 30 mg therapy, although those patients with non-functioning NETs experienced the most benefit. Safety data were consistent with those seen in previous studies of octreotide LAR. While the proportion of patients with extended TTP was highest in those with low HL (≤10 %) versus placebo, subgroup analysis of data from patients with HL >10 % (n=21) revealed that octreotide LAR extends TTP regardless of HL.*(Costa F,et al; Oberg K,et al; Kimura W,et al; Yao JC,,et al; Modlin IM,et al; Lal A,,et al; Bauer W,,et al; Florio T,et al; Susini C,et al; Chadha MK,et al; Theodoropoulou M,et al; Grozinsky-Glasberg S,et al)*

Role of Octreotide in Chemotherapy / Radiation Related Diarrhea

Enrolment criteria permitted patients to have either a functioning (patients that could tolerate symptoms with loperamide and clinical support) or non-functioning tumour: those with symptoms of carcinoid syndrome and increased urinary 5-hydroxyindole acetic acid (5-HIAA) were classified as having a functioning tumour. Hepatic tumour load (HL) was quantified by computed tomography (CT) or magnetic resonance imaging (MRI). *(Costa F,et al)*

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Octreotide in Carcinoid Syndrome

Octreotide is an analog of the polypeptide hormone somatostatin.Octreotide acts on the somatostatin receptors, which couple to phospholipase C via inhibitory G proteins, and causes vascular smooth muscle contraction. The alpha and beta-gamma subunits of the G proteins inhibit adenyl cyclase and stimulate phospholipase C, respectively. At a cellular level, like somatostatin, octreotide induces an increase in calcium entry via L-type calcium channels, which leads to increased calcium-induced calcium release via ryanodine receptor calcium release channels from the sarcoplasmic reticulum in the smooth muscle cells, thus, activating myosin light-chain kinase via its interaction with calcium-calmodulin, and therefore, initiating the contraction cycle. The release of calcium from the sarcoplasmic reticulum is also due to the formation of 1, 4,5-inositol triphosphate, potentiated by phospholipase C. Hence, octreotide, similar to the action of endogenous somatostatin, inhibits the release of hormones from the anterior pituitary gland, including thyroid-stimulating hormone and growth hormone, and hormones of the gastroenteropancreatic endocrine system such as insulin and glucagon.(Debnath D,)

Carcinoid syndrome (CS) is a paraneoplastic syndrome as¬sociated with serotonin secretion, which undergoes renal excretion as 5-hydroxyindoleacetic acid in the urine (u5-HIAA). The goal of this retrospective, observational study was to review a personal series of CS cases by performing a search of the clinical and ultrasound records of patients with metastatic liver disease.

Fourteen patients with CS were identified over a period of 28 years . The mean age was 58 years (range, 40-80 years), 64 % were female and 36 % were male, all of them Caucasians. Given the search method used, all pa¬tients had liver metastases and the primary neuroendo¬crine tumor was located in the bowel (50 %), in the gas¬troduodenal area, in an unknown site (14 %) and in the mesentery, pancreas and lung in 7 % of cases. The tumors were G1-G3 and their clinical manifestation was CS, with flushing and chronic diarrhea. Flushing developed in 86 % of cases, diarrhea in 78 % and heart disease in 21 % of cases. One case included steatorrhea and one case includ¬ed bronchoconstriction (7 %).

Of all 14 patients, ten received treatment with somatostatin analogues (octreotide and lanreotide) in standard doses via the subcutaneous or intramuscular route (1), which reduced symptoms in 70 % and u5-HIAA in 50 % of cases. Liver tu¬mors were reduced in one case (7 %) and primary tumors in the ileum were reduced in 33 % of cases. The main side ef¬fect of treatment was development of bladder lithiasis.

The incidence of CS is 0.27/100,000 in the United States , occurring in 10-25 % of neuroendocrine tumors , pri¬marily in the digestive system (70 %) followed by the respi¬ratory system (25 %). Age at presentation was from 55 to 60 years . The mean age was 58 years.

Flushing develops in 85 % , diarrhea in 80 % (3,4), heart disease in 60 % (other reviews find 20-40 %) , and bron¬chospasm in 10-20 % of cases. Liver metastases are pres¬ent in 87-100 % of cases . Treatment with somatostatin analogues reduces symptoms in 50-80 %, and u5-HIAA in 45-50 % of cases , which is similar to our series. Other treatments include chemotherapy, interferon, everolimus and loperamide for diarrhea. *(Varas Lorenzo M.)*

Other Uses of Octreotide in Malignancy

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is a common complication of intra-abdominal cancer, frequently seen in advanced gastrointestinal and gynecologic cancer. Management of MBO can be challenging, particularly if the patient is not a surgical candidate. No consensus exists on how best to manage these patients medically. Retrospective studies suggest that the combination of dexamethasone, octreotide and metoclopramide may lead to relief of obstruction and improvement in symptoms associated with the obstruction.

"Triple therapy" with dexamethasone, metoclopramide, and octreotide for management of nonsurgical MBO in this small sample size appears safe and well tolerated however a diagnosis of inoperable MBO remains associated with poor prognosis and death within months. *(Walter M)*

Efficacy of octreotide to reduce lymphorrhea and prevent lymphocele after pelvic lymph node excision in gynecological malignancies

Ina study of patients with more than 200 mL of lymph drained per day until postoperative day 3 after pelvic lymph node excision were enrolled. Of the 75 patients, 36 were managed by conservative methods without the injection of octreotide, and the other 39 patients were treated with the injection of octreotide. The treated group was injected with 0.1 mg octreotide q8h for 5 days, starting on postoperative day 3. The drainage tube was removed when the amount of drained lymph decreased to 100 mL per day. The age, BMI, operation time, removed lymph nodes, amount of lymph, duration of drain placement, proportion of patients with lymphocele and complications between these two group were compared.

The total and mean daily amount of lymph produced per patient was significantly lower in the octreotide-treated group than in the untreated group. The duration of drain placement was shorter in the octreotide group than in the untreated group. The proportion of patients with lymphocele in the treatment group was lower than that in the untreated group.

The injection of octreotide is effective to reduce lymphorrhea and prevent lymphocele after pelvic lymph node excision in gynecological malignancies. *(Gao L,et al)*

Octreotide in Conservative Management of Chyle Leak Post Neck Dissection in Cases of Head Neck Cancer:

Chyle leak is a dreadful complication in patients undergoing neck dissections. Octreotide has been used in the management of chyle leak post neck dissections in head and neck cancer patients. Currently there is no consensus and practice guidelines on the same. (1) To study the role of octreotide in early cessation of post neck dissection chyle leak. (2) To study incidence of intra-operative and post-operative CL, its relation to the extent of nodal disease and neck dissection, prior radiotherapy. Retrospective analysis of 16 patients out of 529 neck dissection over a period of 03 years between Jan 2016 and Dec 2019 who developed post-operative chyle leak. All patients who had post-operative chyle leak were administered octreotide. Time taken for chyle leak to stop was primary outcome. Secondary outcomes were duration of hospitalization post-operatively, incidence of intra-operative and post-operative chyle leak, its relation to the extent of nodal disease, prior radiotherapy and type of neck dissection. 59 of 529 neck dissections (11.15%) were noted to have intra-operative chyle leak. 16 of 529 neck dissections (3.02%) developed post-operative chyle leak. On applying chi square test, prior multimodality and N plus neck were found to be significant risk factors in developing postoperative chyle leak. Considering only RT versus no RT in prior multimodality treated group, the difference was insignificant. Onset of chyle leak varied from 1 to 5 post-op day (mean 2.68 days). 15 (93.75%) patients responded to octreotide. Chyle leak resolved between 3 and 10 days (mean 5.18 days) and octreotide was given for 5-12 days (mean-7.18 days). Overall duration of hospitalization ranged from 09 to 18 days (mean 12.18 days). 01 patient (6.25%) had to be re-explored due to high volume leak despite using octreotide. Adverse effects of octreotide were minimal and tolerable. Octreotide is effective in reducing the duration of chyle leak, hospital stay and need for surgical intervention. It may be considered as suitable adjunct to conservative measures in the management for post-operative chyle leak. *(Gupta V,et al)*

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