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Management of Gastrointestinal Carcinoid Tumors: An Overview

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Abstract

Gastrointestinal Carcinoid Tumors are neoplasms that originate in the lining of the gastrointestinal (GI) tract and are derived from the neuroendocrine cells. It is rare for these tumors to be detected before they develop metastases, and they are often discovered incidentally during surgery for other abdominal conditions. Currently, various treatment options are available for managing these tumors, such as surgery, which is usually the most effective treatment. The type of surgery depends on several factors, including the size and location of the tumor, the patient's comorbidities, and the presence of carcinoid syndrome. As a result of the low probability of metastasizing, surgery is typically the best treatment option for neuroendocrine tumors of type I. NETs of type II and III are the most aggressive and require a formal gastrostomy, whereas NETs of type IV are treated with local ablation or cytotoxic chemotherapy. The first line of pharmacological treatment is somatostatin analogs (SSAs); they inhibit hormone production and tumor cell proliferation by binding to G-protein-coupled somatostatin receptors (SSTRs). Another option is Telotristat, which inhibits tryptophan hydroxylase - 1 (TPH-1) in the digestive tract, thereby reducing serotonin production. The treatment of patients with carcinoid syndrome who are refractory to SSAs could be improved by peptide receptor radionuclide therapy (PRRT), which uses radiolabeled somatostatin analogs to target overexpressed somatostatin receptors in well-differentiated NETs.

Keywords: Gastrointestinal carcinoid tumors; Carcinoid tumors; Neuroendocrine tumor; NETs; GI-NETs

Abbreviations: GI: Gastrointestinal; NET: Neuroendocrine Tumor; SSA: Somatostatin Analogs; SSTR: G-Protein-Coupled Somatostatin Receptors; PRRT: Peptide Receptor Radionuclide Therapy; EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Submucosal Dissection; SST: Somatostatin; FDA: Food and Drug Administration; cAMP: Cyclic Adenosine Monophosphate; SHP: Src Homology Domain Phosphatase; IGF-1: Insulin-like Growth Factor 1; VEGF: Vascular Endothelial Growth Factor; 5-HT: Serotonin; TPH-1: Tryptophan Hydroxylase 1; GEP: Gastroenteropancreatic

Introduction

Gastrointestinal Carcinoid Tumors are neoplasms that form in the lining of the gastrointestinal (GI) tract and are derived from the neuroendocrine cells. The majority of neuroendocrine tumors (NETs) occur in the gastrointestinal tract (55%), which includes the small intestine (45%), rectum (20%), appendix (16%), colon (11%), and stomach (7%). NETs account for 2% of all malignant tumors of the gastrointestinal tract. In the United States, the incidence and prevalence of GI-NETs have increased

over the last few decades. This may be attributable to earlier detection, increased awareness, and widespread use of endoscopy and imaging studies for various gastrointestinal disorders. GI-NETs are more common among African Americans than in other population ethnicities [1]. Symptoms and signs may result from the growth of the tumor and the hormones it produces or from the organ affected by it. Clinical manifestations include abdominal pain, nausea, vomiting, diarrhea, constipation, and weight loss. Tumors of this type are rarely detected before metastasizing. They are often discovered incidentally during surgery for another abdominal disorder. Patients presenting with symptoms suggestive of a NET may benefit from the following tests to detect it: Blood Chemistry Study [2], 24-Hour Urine Test, Imaging Tests (Computed Tomography Scan, Magnetic Resonance Imaging Scan, Positron-Emission Tomography Scan, Endoscopy, Biopsy) [3]. In addition, there are several options for managing NETs. In this article, we aim to review the following therapeutic regimens: surgical resection, octreotide/lanreotide, telotristat, and peptide receptor radionuclide therapy (PRRT).

Surgical Resection

Many gastrointestinal (GI) carcinoid tumors can be cured by surgery alone. The type of operation will depend on some factors, including the size and location of the tumor, whether the person has any other serious diseases, and whether the tumor is causing the carcinoid syndrome [4]. To determine the best treatment for different GI-NETs, they are classified into four subtypes based on their histology, morphology, and pathogenesis [5-8]. Due to their low rates of locoregional metastasis (<5%), type I NETs are usually treated with endoscopic resection or watchful waiting to observe symptoms or tumor progression [5,7,9]. Also, antrectomy can be considered in patients with these types of gastric tumors with multiple lesions or in patients who will require frequent endoscopic resection because of progressive, invasive, or recurrent disease [5,7]. Regardless of the treatment method, patients with type I NETs have an excellent prognosis, with an average life expectancy [5]. In general, NETs of type II represent less than 10% of all gastric NETs [5]. The treatment consists of gastrinoma resection, endoscopic resection, and surveillance if the procedure does not extend beyond the submucosa [4,6]. A formal gastrectomy is recommended for type II and III NETs that are invasive beyond the submucosal layer and >2cm in diameter. As a result of the poor prognosis and aggressive nature of type III NETs, lymphadenectomy should also be considered if there are no metastases [5,7,9]. Treatment options for type IV NET include local ablation, systemic somatostatin analogs, or cytotoxic chemotherapy, as these patients have an unresectable or recurrent metastatic disease with a median survival time of eight months [5,9]. Occasionally, patients with type IV NET may be considered candidates for volume reduction surgery or cytoreductive surgery to relieve symptoms, in addition to a cholecystectomy to avoid the development of biliary sediments resulting from somatostatin therapy [9]. Endoscopic resection has been the preferred method of removing carcinoid tumors from places such as the duodenum, depending on the tumor's shape and location.

However, surgical resection should be considered in tumors larger than 2cm, including local excision in conjunction with or without locoregional lymph node sampling or pancreaticoduodenectomy due to the possibility of nodal dissemination [7,9]. The preferred approach for NETs of the small intestine is complete oncological removal of the primary tumor and mesenteric adenopathy [7]. In the case of NETs of the appendix, appendectomy is recommended for tumors less than 20millimeters. In comparison, tumors more significant than 20 millimeters should undergo right hemicolectomy due to their association with lymph nodes and distant metastases [6,7,9]. Lastly, for colorectal NETs, colectomy accompanied by lymphadenectomy is recommended, except for those ⩽10millimeters, which are treated with conventional endoscopic mucosal resection (EMR), modified EMR, or endoscopic submucosal dissection (ESD), since their long-term prognosis with these treatments is favorable [7,9,10].

Octreotide/Lanreotide

Somatostatin (SST) has long been known as one of the principal inhibitors of exocrine and endocrine hormone secretion [11,12]. Consequently, SST synthetic analogs (SSAs) have been developed and have demonstrated positive results in clinical applications, such as treating NETs. There are three SSAs approved by the Food and Drug Administration (FDA) that have been used in clinical practice, and they are classified as first-generation (octreotide and lanreotide) and second-generation (pasireotide) SSAs [11-13]. Octreotide was the first SSA approved by the FDA, and it can be administered subcutaneously or intramuscularly. The subcutaneous presentation consists of 50, 100, or 200mcg and can be given every 8 to 12 hours, while the intramuscular presentation consists of 10, 20, or 30mg every 28 days [12,14].

In contrast, lanreotide formulations were initially administered intramuscularly at doses of 30 or 60mg every 7-14days but were later switched to subcutaneous administration at doses of 60, 90, or 120mg every 28 days. In 2017, Lanreotide was approved for treating Carcinoid Syndrome in the United States [12]. Because of their inhibitory effects, first-generation SSAs are considered first-line treatment options in carcinoid tumors, the most common NETs in the gastrointestinal tract [11]. SSAs can regulate hormone secretion and tumor cell proliferation by binding to G-protein-coupled somatostatin receptors (SSTRs), which are divided into five receptor subtypes (SSTR1 – SSTR5). The SSTR2 and SSTR5 are the predominant subtypes in endocrine tissues and are widely expressed in NETs [11,12]. In the antisecretory effect, the complex (SSA-SSTR) inhibits adenylyl cyclase and voltage-dependent calcium channels, decreasing cyclic adenosine monophosphate (cAMP) and intracellular calcium levels and subsequently inhibiting hormone secretion [11-14]. In addition, SSA has direct and indirect antiproliferative effects. It causes pro-apoptotic

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effects and inhibits cell proliferation by activating Src Homology 2 Domain Phosphatase-1 (SHP-1) and SHP-2, respectively.

On the other hand, SSA indirectly inhibits circulating growth factors, such as insulin-like growth factor 1 (IGF-1), IGF-2, vascular endothelial growth factor (VEGF), and tumoral angiogenesis [12]. Due to their ability to inhibit serotonin secretion, SSAs have been widely used to reduce carcinoid symptoms, such as diarrhea, flushing, and wheezing, and improve general health. Additionally, they have been used as a treatment for well-differentiated, locally advanced, or metastatic NETs due to their antiproliferative effects [11,12]. Even though adverse reactions are common and usually occur at the beginning of the treatment with the administration of initial doses, they improve over time with continuous doses [12,13]. The most common adverse reactions are diarrhea and gallbladder abnormalities, such as cholestasis and cholelithiasis. Other common adverse reactions include nausea, vomiting, stomachache, headache, skin erythema and pain at the injection site, hyperglycemia, and hypothyroidism [12-14]. It has rarely been associated with upper respiratory symptoms, fatigue, depression, weakness, alopecia or hair loss, visual abnormalities, arthralgias, or lower back pain [14]. It has not been shown that increasing the dose of SSAs worsens adverse reactions compared to regular doses [12]. SSAs are contraindicated for individuals with hypersensitivity to SSAs and in pregnant or breastfeeding women due to a lack of information [13]. It should be used with caution in patients with renal or liver failure, a history of cholestasis or cholelithiasis, hyperglycemia or diabetes mellitus, and severe congenital heart disease. Therefore, these patients should be monitored when using SSAs [13]. The use of SSAs has been demonstrated to be safe and effective. It is important to note, however, that long-term use of SSAs may cause resistance to treatment [11,12].

Telotristat

A common symptom of carcinoid syndrome is diarrhea, which is caused by elevated levels of serotonin (5-HT), which stimulate peristalsis and bowel secretion [15]. Serotonin is produced in the gastrointestinal tract by converting tryptophan into serotonin by tryptophan hydroxylase. Telotristat, another option for treating symptoms associated with GI carcinoid tumors, inhibits the enzyme tryptophan hydroxylase 1 (TPH-1), explicitly expressed by enterochromaffin cells. This results in a peripheral reduction in the production of serotonin in the gastrointestinal tract [15,16]. It is orally administered as a prodrug and hydroxylated into its active metabolite by carboxylesterases [17]. *In vitro* studies state there is a low drug-to-drug interaction as it is not a substrate for CYP enzymes, and its properties are not affected by age, gender, or renal or mild hepatic impairment [3]. Dual treatment is used as a coadjutant of SSA in patients with >4 bowel movements daily [16]. The currently approved dosage by the National Comprehensive Cancer Network guidelines is 250mg three times daily in patients with poorly controlled carcinoid syndrome [16,17]. Safety analysis data from two studies report no serious adverse effects; some patients experienced gastrointestinal symptoms (nausea and constipation), and others had mild depression [17]. Furthermore, most patients referred to an improved quality of life, as bowel movement frequency decreased significantly [15-17]. Therefore, this new medication received global approval on February 28th, 2017, as it reduces bowel movements, improves life quality, and is generally well-tolerated without significant side effects [16,17].

Peptide Receptor Radionuclide Therapy

Despite optimal treatment with SSAs, patients may still experience diarrhea and flushing, particularly in severe cases [18]. Thus, peptide receptor radionuclide therapy (PRRT) has been considered a second-line treatment option for carcinoid syndrome refractory to SSAs [18-20]. Furthermore, PRRT with 177Lu-DOTATATE was approved in 2018 by the FDA for treating gastroenteropancreatic NETs (GEP-NETs), administered intravenously. PRRT uses somatostatin analogs, such as Octreotide (DOTATOC) and octreotate (DOTATATE), radiolabeled with a radioactive material (Lutetium-177). They target somatostatin receptors, which are highly expressed in well-differentiated NETs. Therefore, PRRT is indicated for patients with advanced inoperable well-differentiated GEP-NETs [18-20]. Although PRRT is well-tolerated, the most common adverse reactions reported are nausea and vomiting. Adverse reactions are frequently associated with the amino acid solution given to protect the kidneys rather than with the medication itself [18]. Other common adverse reactions include temporary hair loss, anemia, leukopenia, thrombocytopenia, acute kidney injury, and liver injury [20]. Even though the exact dose and time are not established, prophylactic octreotide 500μg/hour intravenously preoperative, intraoperative, and postoperative are recommended to prevent carcinoid crisis [19]. PRRT is contraindicated during pregnancy and breastfeeding and in patients with impaired hematological, renal, hepatic, and cardiac functions [21]. Despite the carcinoid crisis and adverse reactions, PRRT is an effective, safe, well-tolerated, and viable treatment option for advanced well-differentiated GEP-NETs.

Conclusion

Advances in modern medicine have accelerated new forms of multimodal approaches for treating gastrointestinal cancer. Therefore, the opportunity for precise care management is present, thus a better outcome for most patients. This article's interest is to directly overview various therapeutic regimens aimed at comparing them at different GI-NET stages. In this perspective, the effectiveness of the selected strategy proves to be influenced by the grade of locoregional compromise, histology, morphology, and pathogenesis of the carcinoid tumor. Our data finds surgical techniques to optimally treat many subtypes (I-IV) of locoregional carcinoid tumors and improve the patient's symptomatology caused by elevated serotonin levels (5-HT). In addition, surgical approaches have been shown to have higher risk reduction and a good prognosis. As reported by previous data,

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GI-NETs cases treated with FDA-approved systemic and radiation therapy are well-tolerated and effective in most cases, although not fully understood nor indicated in specific cases, pregnancy, previous organic failure, and undifferentiated tumors. Accordingly, managing NETs with first-line therapies such as SSAs has remarkable outcomes in a widespread clinical scenario. Moreover, our team recognizes the importance of precise multidisciplinary assessment of patients, especially in cases where life quality is compromised due to advanced carcinoid symptoms. Therefore, we recommend the discussion of adverse effects and life quality improvement before the intervention, as further research in surgical and system strategies to propel success as a primary outcome.

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