Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.4854

INTERVENTIONAL THERAPIES IN CARCINOID HEART DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract
Carcinoid heart disease is a rarely occurring cardiac manifestation that typically affects the right-sided heart valves and ultimately results in right heart failure, and it occurs in patients with advanced neuroendocrine tumors and the carcinoid syndrome. Online databases such as Midline, Google Scholar, and the PubMed databases, were searched using the following methodology to find papers regarding the therapies of carcinoid heart disease**.** Relevant publications were evaluated for study quality and evaluate by independent reviewers. Treatment type was taken into account when stratifying the meta-analysis of the intervention's effects on symptoms connected to carcinoid heart disease. 3682 treatment interventions on outcomes unique to carcinoid heart disease were gathered from 93 research, according to our results. The study's overall quality was poor because it included just six randomized controlled clinical studies. Octreotide and lanreotide, two somatostatin analogs, improved symptoms in 65–72% of patients and caused a biochemical response in 45–46% of them. In 72–84% of cases, flushes and/or diarrhea were reduced as a result of an increase in dosage, frequency, or interclass transition. In 82% of carcinoid heart disease patients with a liver-dominant disease, liver-directed therapy can alleviate symptoms, according to a retrospective institutional series. 40 percent of patients with diarrhea resistant to somatostatin analogs experienced a reduction in bowel movements after taking the serotonin synthesis inhibitor telotristat ethyl. In 45–63% of instances, interferon-alpha was able to control the carcinoid heart disease symptoms. After radionuclide therapy, favorable response has been shown in subgroup analyses of studies that do not explicitly involve patients with carcinoid heart disease. In the carcinoid heart disease, chemotherapy and everolimus did not provide a noticeable effect. We conclude that patients with carcinoid heart disease can get numerous courses of treatment. It is highly recommended to start randomized controlled studies using carcinoid heart disease symptoms as the primary outcome.

Keywords: Carcinoid heart disease, Interventional therapies, Neuroendocrine tumors

Introduction

Carcinoid heart disease occurs in rare neuroendocrine tumors producing carcinoid syndrome. Carcinoid tumours are most often located in the gastrointestinal system, though they can also occur in the bronchopulmonary system (1).

Patients may have symptoms from a range of biologically active substances that are produced by neuroendocrine tumors (NETs) (2). Carcinoid heart disease is a well-known example of a hormonal problems brought on by active NETs. The condition was first identified in 1931 and is characterized by prolonged fibrotic changes in the mesentery and heart valves, as well as increased bowel motions, vasoactive flushes, and bronchospasms (3). Serotonin, an amine derivative, is considered to be the primary mediator of carcinoid-related sequelae, including diarrhea and fibrosis (5-hydroxytryptamine). Bradykinins, tachykinins, histamine, and other co-secreted peptide hormones and amines have also been linked to NET patients' cutaneous flushing and respiratory issues (4).

Usual dictum is that right sided heart valves are involved when the tumour has metastasized to the liver as liver acts as the first filter for the products secreted by the tumour, mainly serotonin (5-hydroxytryptamine, 5-HT) (5). Other products of neuroendocrine tumours include tachykinins, kallikrein and prostaglandins. Severe involvement of right sided heart valves can lead to heart failure. Left sided heart valves can be involved when there is tumour in the lungs as lungs are the second filter for the products of carcinoid tumour (6).

Individuals who have midgut NETs are more likely to experience carcinoid heart disease, while it can also occur in people with NETs of different origin (7). It is crucial that the released vasoactive molecules enter the systemic circulation directly, avoiding the portal circulation, as the liver will actively degrade and deactivate them (8). This indicates that 5-hydroxyindolacetid acid (5-HIAA), an inert substance, is produced by the metabolism of all serotonin in the portal vein (9). Although bone, lymph nodes, and the liver can all receive metastases from gastroenteropancreatic NETs, patients with liver metastases are typically diagnosed with carcinoid heart disease (10).

As a result, most carcinoid heart disease patients are not amenable to treatment intended to be curative. Thus, in this patient population, carcinoid heart disease management plays a significant role in palliative care (11). Over time, numerous therapeutic approaches have been developed to treat carcinoid heart disease, including as targeted radionuclides, liver-directed therapy, chemotherapy, interferon alpha (IFN), somatostatin analogs (SSAs), and medications that disrupt the serotonin system (12). The aim of this systematic review and meta-analysis is to summarize the available data on interventional therapies in Carcinoid heart disease in different data basis.

Methodology

Searching Methodology

On February 10, 2024, online databases such as Midline, Google Scholar, and the PubMed databases, were searched using the following methodology to find papers regarding the therapies of carcinoid heart disease: Carcinoid heart disease, Therapy, Malignant and carcinoid and Heart disease and therapy separately.

Articles Screening

A total of 1483 records were identified on the databases in which Records removed before screening included 260 duplicate records, 180 records marked as ineligible by automation tools, and 222 records removed for other reasons. The records screened after the duplicates were removed was 821. Out of 821, 401 records were excluded because in it, 5 were animal studies, 02 case reports/series, 38 related to NET diagnosis, 18 guidelines, 23 related to heart disease, 26 related to other diseases, 20 preclinical studies, 217 reviews, and 52 unrelated treatment records. The remaining 401, sorted for retrieval were again looked for reports that were not retrieved, which was N=244, and the remaining were counted to be 176. In the remaining 176, full-text publications that did not specifically address carcinoid heart disease or had qualitative results were excluded (n =83). The study remained after was became limit to 93 pure research articles which were included in our study for meta-analysis.

It was determined that retrospective series or single arm therapy studies were also appropriate for inclusion due to a lack of randomized controlled trials. Publications without quantitative outcome data or without a description of particular symptoms in the patient selection process with carcinoid heart disease were excluded. As a result, research that solely detailed an intervention's antiproliferative effects without providing clinical or biochemical information unique to carcinoid heart disease

patients was likewise disqualified. A total of 93 publications that satisfied the inclusion criteria for the meta-analysis were found through this review. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was followed in the evaluation process (13). The approach of selecting studies is shown in **Figure 1**.

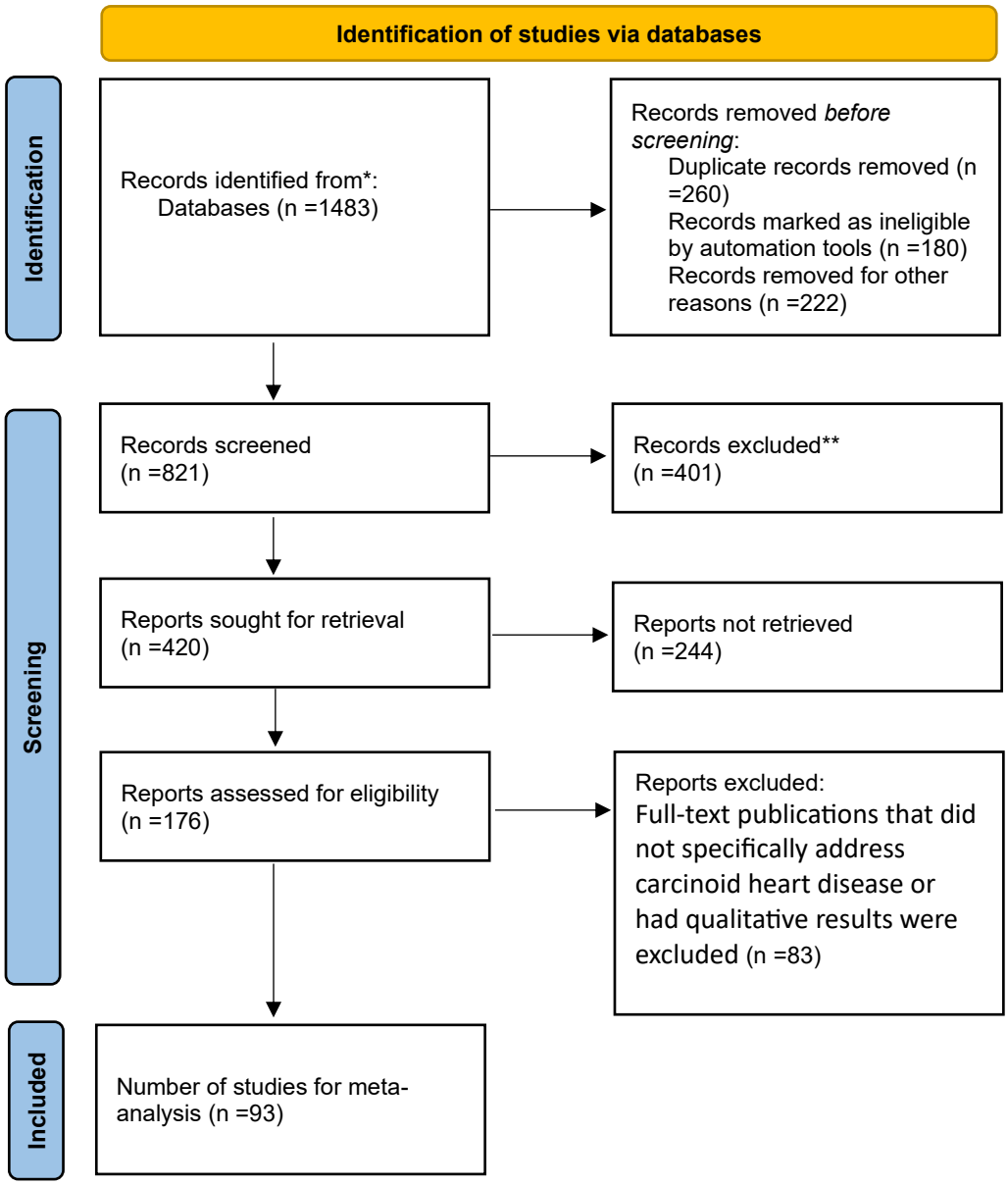

Figure 1: A detailed flow chart diagram of study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data Extraction and Analysis

Cochrane Guidelines were used to score the full-text articles on a standard form used for data extractions (14). Publications were graded on a low, medium, or high scale representing the quality of the publication for a number of items related to reporting bias, performance, and selection as a methodological quality indicator. The inclusion and randomization criteria descriptions were used to score selection bias. By examining descriptions of a control arm and allocation concealment, performance bias was evaluated. Selective reporting, partial data management, industrial sponsorship, and biased reporting were all given different scores. During several teleconferences, the topics of eligibility requirements and reporting uniformity were covered. A third author (W T Z) examined discrepancies in the two reviewers' scores before rendering a final judgment.

Publications were categorized into six groups based on the available therapeutic options: serotonin pathway inhibitor, liver-directed therapy, IFN, SSA, radiation therapy, and chemotherapy. Data for a group receiving a placebo were also collected. Efficacy outcome data were collected as the proportion of patients who had a clinical or biochemical response to a particular intervention for the purposes of meta-analysis. Clinical response included flushes and/or diarrhea symptoms in addition to overall symptom reduction. Data on alternative biomarkers (such as chromogranin-A or gastrin) were not included in the evaluation of the biochemical response, which was precisely measured as change in urinary 5-HIAA excretion. Although they were measured, other (surrogate) outcomes like quality of life, circulating serotonin levels, bronchoconstriction, and stool consistency lacked enough information to be included in a meta-analysis. Because of the often-uneven reporting of this outcome for symptom or biochemical control, the duration of response was not noted. Prism version 7 was used for statistical analysis.

Results

Prospective studies were surpassed by single-center retrospective series, which carried a significant risk of exaggerating the effectiveness of a particular treatment method in patients. However, the majority of prospective studies including carcinoid heart disease patients did not have a control group or blinding of the patient and researcher. Studies included patients with non-functional pancreatic NETs, functional pancreatic NETs, and syndromic pancreatic NETs in significant numbers in addition to carcinoid heart disease patients. Of the research that were funded by the industry and published after 2005 (15), just six had a randomized controlled design and concentrated on outcomes particular to carcinoid heart disease.

Liver-directed therapies

A sequence of a multitude interventional procedures, including as cryosurgery, radiofrequency ablation, bland embolization, chemoembolization, or radioembolization, were used in the studies. Hepatic interventions in 25 studies, including 579 individuals, were gathered for the meta-analysis. There is a substantial bias in interpreting the results of liver-directed therapies because patients were frequently receiving treatment with other modalities, such as SSAs, concurrently. The majority of trials just reported the clinical response; no additional manifestations or quantification was provided. Just 2 of the 22 studies on liver-directed treatments used diarrhea or flushes to stratify the symptom changes (16, 17).

Clinical and biochemical response rates have often been reported to be high, particularly in the very small series. Urinary 5-HIAA levels were considerably decreased in 116 out of 191 (61%) patients, whereas 393 out of 479 (82%) patients experienced a symptomatic response as a result of the combination of the several liver-directed modalities. Most of the studies focused on treatments involving radioembolization, chemoembolization, or bland emboli. Response rates for total symptoms and serotonin release when all embolization procedures are combined are 82 and 63%, respectively (16, 18). Notably, patients who have already received SSA treatment do not seem to have any further decrease in efficacy.

Chemotherapy

Research assessing the impact of chemotherapy on carcinoid heart disease commenced in the 1960s. The majority of publications on chemotherapy for malignant carcinoid heart disease date back before 2000, yet because of the uneven reporting of carcinoid heart disease specific results, these studies were not included in the current meta-analysis. Unfortunately, the majority of chemotherapy-based research limits the scope of their findings to the biochemical reaction (19). Following chemotherapy regimens involving combinations of streptozotocin, cyclophosphamide, platinum derivatives, or 5-fluoruracil, the observed 5-HIAA response rates are 31% in 111 individuals overall (range 0-71%). Only the clinical response data for cisplatin (0%), cyclophosphamide and methotrexate (6.7%), and lomustine and 5-fluoruracil (60%) are available. Additionally, research also describes the notable adverse effect profiles that patients receiving these varied regimens experienced (20).

Everolimus is registered as an antiproliferative therapeutic option for progressing NETs, although not being classified as chemotherapy. In the RADIANT-2 trial, 81 out of 140 patients (61%) with midgut NET and hormonal complaints responded biochemically to octreotide LAR plus everolimus, while 76 out of 141 patients (54%) received octreotide LAR alone (21). However, the everolimus plus octreotide LAR group saw a greater rate of diarrhea (27 vs. 16%). After adding everolimus to octreotide, a small retrospective study revealed improvements in diarrhea or flushes in 6 out of 10 and 5 out of 7 individuals with refractory carcinoid heart disease symptoms, respectively (22).

Somatostatin analogs

Different formulations of octreotide and lanreotide have been thoroughly studied in patients with carcinoid heart disease since the introduction of SSAs. Both analogs are considered first-line treatment for carcinoid heart disease in unresectable and/or metastasized NE, primarily targeting the somatostatin receptor subtype 2 (17). More recently, octreotide LAR and lanreotide autogel were registered as antiproliferative treatments for use in patients with NETs worldwide as a consequence of the outcomes of exceptional double-blind placebo-controlled trials examining the antiproliferative properties of these medications (17). Though patients with the carcinoid heart disease were not included in the CLARINET study, the PROMID study lacked data on symptomatic or biochemical control for a subset of patients with the carcinoid heart disease (Figure 2).

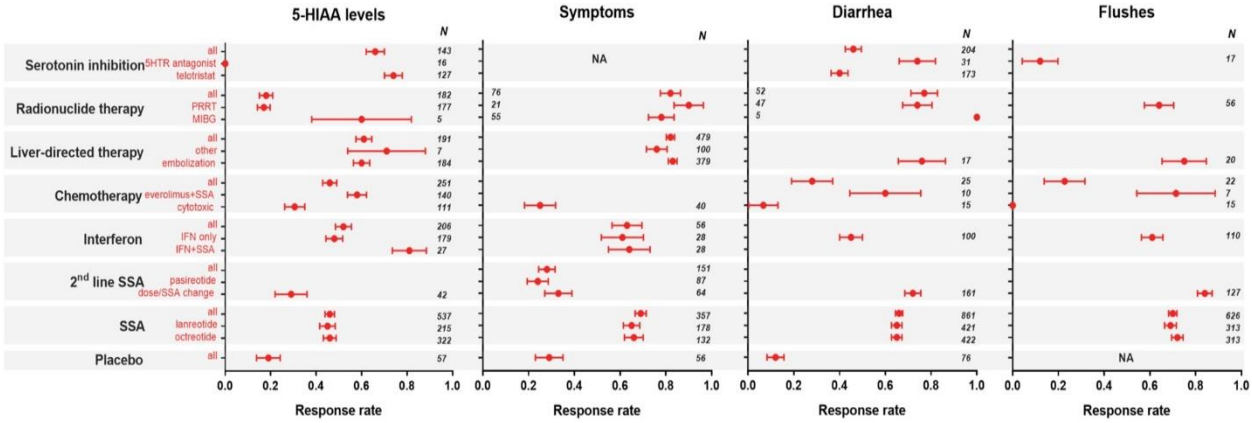

Figure 2: Meta-analysis of treatment results for carcinoid heart disease-targeting interventional therapies.

This meta-analysis has gathered 1945 interventions that were documented in 33 trials using these SSAs in patients with carcinoid heart disease. In these studies, a large number of patients (range 0-92%) who were starting on SSAs had previously received pre-treatment with various SSA formulations (23, 24). A special study into the escalation in SSA dose/frequency or SSA switch following progression under a regular dose of SSA was conducted in six studies involving 378 participants. Among them, 72 completed a transition to pasireotide, a multi-somatostatin receptor-targeting analog. Each of these studies of second-line therapy was assessed independently (25).

Octreotide caused a response in 66% of participants with general symptoms, 65% with diarrhea, and 72% with flushing after starting of therapy. The response rates of 65, 65, and 69%, respectively, were comparable among carcinoid heart disease patients treated with lanreotide. In 66–70% of patients, management of the most pertinent carcinoid heart disease elicited symptoms was achieved when paired with retrospective studies involving the administration of both analogs. In 45–46% of carcinoid heart disease patients treated with either SSA, on the other hand, the biochemical response of 5-HIAA levels was lower (26). In terms of assessing carcinoid heart disease control, overall effects were similar across all formulations or analogs. These projected percentages are consistent with the response rates found in the prospective studies with larger patient numbers and better design quality.

Two retrospective studies assessed dose escalation in the context of second-line therapy following SSA, while two prospective trials investigated the effects of reducing the injection interval to 21 days or switching to an alternate SSA. 116 out of 161 individuals (72%) and 107 out of 127 patients (84%)

experienced less flushes as a result of these measures. These trials showed a less substantial biochemical reaction, at 29%. In contrast, two studies conducted on carcinoid heart disease patients who were not responding to octreotide or lanreotide showed that a switch to pasireotide by an SSA only produced a symptomatic response in 21 out of 87 (24%) of the patients. There was little information available about 5-HIAA levels, diarrhea, or flushing in individuals who were refractory to pasireotide (27, 28).

Placebo

There were only four trials with a placebo treatment arm that reported on biochemical or symptomatic carcinoid heart disease results. In one research assessing lanreotide, an SSA, and three studies involving patients who had refractory diarrhea to SSAs treated with telotristat ethyl, 132 individuals got placebo treatment collectively. In these groups, there was a small but noticeable placebo effect, with 9 out of 76 patients (12%) reporting less diarrhea and 16 out of 56 patients (29%) reporting a symptomatic response. Furthermore, 11 out of 57 patients, or 19% of the total, experienced a decrease in 5-HIAA levels of more than 30% (29).

Interferon-alpha

The first observations regarding IFN's positive impact on carcinoid syndrome date back to 1983. Research on patients receiving IFN treatment has concentrated on controlling the symptoms of carcinoid heart disease as well as its proliferation. Notably, the majority of studies have reported fatigue, fever, and flu-like symptoms that affect most patients, which makes IFN less tolerable.

Data was gathered on 347 individuals who were treated with various IFN formulations and combinations throughout 16 studies. The impact of adding IFN to immediate-release octreotide was assessed in a single randomized controlled trial. There was no statistically significant additive effect of IFN on top of the SSA when examining the carcinoid heart disease related outcomes in this multicenter trial, which comprised 39 patients with carcinoid heart disease. The reported response rates of IFN monotherapy varied greatly between 0–90% and 50–80% for clinical and biochemical control, respectively, in four single-arm prospective studies involving 73 carcinoid heart disease patients (30). All IFN trials combined, including those with co-treatment with chemotherapy or SSA, have response rates of 63, 45, 61, and 52% for overall symptoms, diarrhea, flushes, and 5-HIAA levels, respectively.

Radionuclide therapy

The majority of patients receiving systemic treatment for NETs with radiolabeled compounds have a progressing disease. ^{131}Iodine-labeled metaiodobenzylguanidine (^{131}I-MIBG) and 177Lutetium (^{177}Lu) or ^{90}Yttrium (^{90}Y) labeled SSAs are among the available options. A total of 48 patients from four series, including one prospective research, have had the effects of ^{131}I-MIBG on CS-specific outcomes reported (31). Thirteen to one hundred percent of patients had SSAs as a pretreatment. Only the overall symptom outcome—which was resolved in 43 out of 55 patients, or 78%—was included in the ^{131}I-MIBG meta-analysis.

When midgut NET patients are progressing on a regular SSA dose, ^{177}Lu-DOTATATE combined with peptide receptor radionuclide treatment (PRRT) is an effective antiproliferative therapy. Numerous institutional series have shared their experiences with radiolabeled SSAs, however there is an absence of data about carcinoid heart disease therapy specifically (32). 156 patients with carcinoid heart disease specific results following therapy with either ^{177}Lu-DOTATATE or 90Y-DOTATOC were chosen from four prospective phase 2, single-center studies through the systematic evaluation. Out of the 177 individuals that were available, 17% had an inadequate overall biochemical response. However, 74% of the 47 patients who experienced diarrhea and 64% of the 56 patients who experienced flushing showed more encouraging clinical improvements. Despite a high rate of pre-treatment with non-radioactive SSAs (64–100%), these clinical outcomes were achieved (33).

Serotonin pathway inhibitors

Studies have assessed the suppression of serotonin production or action because serotonin plays a significant role in the clinical symptoms within the carcinoid heart disease spectrum. Two prospective trials involving individuals with refractory carcinoid heart disease have assessed the serotonin receptor antagonists ondansetron and cyproheptadine (8). Anti-diarrheal effects were observed in 6 out of 6 patients receiving ondansetron and in 6 out of 12 patients getting cyproheptadine. As anticipated, there was no biochemical reaction. Ondansetron's effectiveness in treating refractory bowel symptoms was validated in 11 out of 13 carcinoid heart disease patients by recent retrospective research.

Recently, patients with carcinoid heart disease who were resistant to SSAs participated in a series of phase 1-3, multicenter, placebo-controlled, double-blind clinical trials to evaluate telotristat ethyl, a new serotonin synthesis inhibitor. In the phase 1-2 trials, patients receiving telotristat ethyl showed anti-diarrheal and biochemical responses in 33 and 31% of cases, respectively. individuals with either four or less stools per day were the focus of the phase 3 trials that examined the safety and effectiveness of telotristat ethyl in individuals with uncontrolled carcinoid heart disease. In both trials, telotristat-treated patients showed a considerably stronger biochemical reaction than placebo-treated patients (34). Compared to 0–20% of patients treated with a placebo, 40–44% of patients showed improvement from telotristat ethyl on diarrhea.

Discussion

A hormonal disorder known as the carcinoid heart disease is brought on by the release of peptides and amines that promote fibrosis, vasodilatation, and gastrointestinal motility (35). Well-designed clinical trials assessing the effectiveness and safety of surgical or medicinal therapies on CS-induced symptoms are rare because of the disease's uncommon incidence. The fact that the first carcinoid heart disease specific RCT was published just 13 years ago serves as an example of this. Rather, the majority of data that have been published relate to institutional experience, single-arm studies that have a small number of patients, or subgroup analyses that are part of larger studies that include non-functional NETs. This makes it more difficult to decide on the best course of action for patients with carcinoid heart disease based on data. We make an effort to contextualize the data we've gathered and offer a carcinoid heart disease patient treatment plan based on the data at hand. Importantly, as this systematic review only assessed the effects of symptoms or serotonin production, we will not be recommending the best course of oncologic therapy (36). Because the available treatment options may have both antihormonal and antiproliferative effects, the hormonal syndrome should always be evaluated in the clinical setting in conjunction with the tumor bulk, primary localization, tumor grade and stage, tumor growth rate, and prior response to therapy. A broader differential diagnosis of diarrhea in NET patients should also be taken into account. This includes drug-induced diarrhea, infection, steatorrhea resulting from exocrine pancreatic insufficiency, postoperative short bowel syndrome, and bile malabsorption (37).

For many years, SSAs have been the main carcinoid heart disease treatment. Although there were no randomized clinical trials conducted when they were first introduced, the majority of carcinoid heart disease patients have convincing data supporting their treatment success (38). The results of our meta-analysis indicate that octreotide and lanreotide, the two main SSAs, have equivalent efficacy in treating clinical response rates in 65–70% of carcinoid heart disease patients. Despite the inclusion of more recent research, these results are consistent with the 2010 meta-analysis on SSAs in carcinoid heart disease that was previously published. First-line therapy for controlling the hormonal consequences of carcinoid heart disease is octreotide and lanreotide due to their efficacy and excellent safety profile.

Although daily subcutaneous injections are equally effective, patients prefer the long-acting, monthly intramuscular or deep subcutaneous injections. Preoperative SSA beginning should be considered mandatory for all symptomatic patients, including in the event of a potentially curative NET resection (which is frequently metastasized). Importantly, in order to avoid a carcinoid crisis, octreotide

perioperative infusion should also be started in carcinoid heart disease patients who exhibit symptoms (39).

A number of strategies have been studied during SSA therapy following the development of clinical symptoms. Studies have assessed analog switches or increases in injection frequency or dose up to high or even ultra-high doses because there is no established maximum limit for SSA dosing. These treatment modifications represent a useful alternative as, if tolerated, they may be able to reduce symptoms in as many as 84% of patients without causing additional harm (40). Daily injections of short-acting "rescue" SSA in addition to long-acting SSA show positive results for a subgroup of patients. It doesn't seem like there are any extra advantages to switching to pasireotide, which targets many receptors. As a result, pasireotide medication is not currently recommended for carcinoid heart disease patients who are refractory, as its clinical response rates are comparable to those of patients who received placebo treatment.

Considering the liver's primary role in the hormonal outflow of carcinoid heart disease and the correlation between endocrine activity and tumor volume, numerous centers have employed surgical or embolization procedures to significantly reduce tumor size and thereby reduce hormonal symptoms (41). Although the response rates are remarkable, there is a serious risk of reporting bias for successful cases due to the retrospective nature of 21 out of 22 studies. Periprocedural complications and long-term adverse events, such as liver failure, should be considered, even though they are not included in the meta-analysis. From the early research on hepatic artery ligation and embolization with 17–27% mortality, procedure safety has significantly improved. Therefore, depending on the liver anatomy and tumor localizations in liver-dominant, refractory carcinoid heart disease patients, liver-directed therapy may be taken into consideration. The following options have an abundance of clinical experience: radiofrequency ablation, bland embolization, chemoembolization, and surgical resection. Selective internal radiation therapy using ^{166}Ho- or ^{90}Y-labeled microparticles for hepatic artery embolization is a modern approach. Despite these limitations, the meta-analysis was unable to demonstrate that one treatment was more effective than the other (42).

Conclusions

The majority of research with poor-to-moderate design has reported on the effectiveness of treatments aimed at treating carcinoid heart disease. Despite this caution, most patients may overcome their hormonal production and complaints with a variety of therapeutic choices. After first-line therapy with SSAs, a number of second- or third-line choices with a tolerable degree of success are selected depending on the unique characteristics of each patient.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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