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Carcinoid-syndrome: recent advances, current status and controversies

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Abstract

Purpose—To review recent advances and controversies in all aspects of carcinoid-syndrome.

Recent findings—Over the last few years there have been a number of advances in all aspects of carcinoid syndrome as well as new therapies. These include new studies on its epidemiology which demonstrate it is increasing in frequency; increasing insights into the pathogenesis of its various clinical manifestations and into its natural history: definition of prognostic factors; new methods to verify its presence; the development of new drugs to treat its various manifestations, both initially and in somatostatin-refractory cases; and an increased understand of the pathogenesis, natural history and management of carcinoid heart disease. These advances have generated several controversies and these are also reviewed.

Summary—There have been numerous advances in all aspects of the carcinoid syndrome, which is the most common functional syndrome neuroendocrine tumors produce. These advances are leading to new approaches to the management of these patients and in some cases to new controversies.

Keywords

neuroendocrine tumor; carcinoid-syndrome; somatostatin; telotristat; PRRT

INTRODUCTION

In all current NET classifications, it is recommended that both pancreatic(neuro)endocrine tumors(pNETs) and NETs in other locations, including the lung and gastrointestinal NETs(GI-NETs)(carcinoids), which comprise 70% of all NETs, be classified as neuroendocrine tumors(NETs)[1].

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Conflicts of Interest

None

NETs in all locations including both pNETs and GI-NETs(carcinoids), can present unique problems in their management, which are rarely seen with other more frequent neoplasms such as adenocarcinomas/lymphomas/etc. One of the most unique aspects of NETs management is they not infrequently require dealing with two management problems: the management of the NET itself, because a proportion pursue aggressive growth, and management of a hormone excess-state, which can occur in in up 30% of pNETs and 3–13% of patients with GI-NETs(carcinoids)[2, ••3]. Whereas, a curative resection would treat both problems, in many cases, because advanced metastatic disease is present, this is not possible, and therefore treatment is required for each of these two problems[2–4].

Carcinoid-syndrome is the most frequent of the NET ectopic hormonal syndromes and is the second oldest, being described with its association with small bowel NETs likely due to ectopic secretion of serotonin in 1954[5], 52 years after insulinomas were described, and one year before Zollinger-Ellison syndrome was described[6]. Carcinoid-syndrome has long fascinated physicians because of the floridness of the symptoms and their variability. However, in many patients the treatment has been frustrating because the carcinoid-syndrome symptoms may be difficult to control[••3,7–12]. Increasing insights into its pathogenesis have occurred, however, relatively few new treatments, or few controlled trials occurred until the last decade or more recently. In the last few years there have been several developments which have allowed better treatments for patients with carcinoid-syndrome[•13,14–16,•17,18–21]. These including long-term studies with long-acting somatostatin analogues[•17,••22,23–30]: the recent release of the tryptophan hydroxylase 1 inhibitor, telotristat[31–35]: studies defining different approaches in patients with somatostatin refractory disease[••3,7–10,12,36–38]: the use of peptide radioreceptor therapy[PRRT] using radiolabeled somatostatin analogues both for control of the carcinoid-syndrome and for tumor growth[••3,••39,40]: the use of ^{131}MIBG(meta-iodobenzylguanidine) both for control of the carcinoid-syndrome and for tumor growth[••3,23,41] as well as other therapeutic approaches including liver-directed therapies(radioembolization, chemo-embolization/embolization) [••3,•17,42–49]: the uses of mega-doses of somatostatin analogues[••3,7–11,50]: the use of new somatostatin analogues such as pasireotide[12,21,37]: surgical debulking and radiofrequency ablation[••3,•17,23,•51,] and use of other tumoricidal agents[••3,•17,23,52,53]. There have also been recent studies on the epidemiology of carcinoid-syndrome[54–57]:other non-classical manifestations of carcinoid-syndrome[•58,59–61], quality of life studies and health care cost studies in patients carcinoid-syndrome[29,62,•63,64–69]: advances and difficulties in the diagnosis of carcinoid-syndrome[70–73] and in the treatment of carcinoid heart disease[•74,75,•76,77–80]. Several new, as well as old controversies remain, but recent studies provide some insights. Each of these areas will be reviewed in this paper concentrating on data from the last 3 years, although a review up to 7 years was done and on some points this data is also included. Not covered in this review are recent studies on pNETs functional syndromes, or studies only dealing with the growth or extent of GI-NET(carcinoid) tumor per se either containing patients with nonfunctional carcinoids, or if carcinoid-syndrome was present in some patients, then without relating the changes to their effect on the carcinoid-syndrome[••39,81–83].

CARCINOID-SYNDROME: ADVANCES, RECENT INSIGHTS, CONTROVERSIES

Carcinoid-syndrome: epidemiology

Classically, carcinoid-syndrome developed in 8% of 8,876 patients with carcinoids[84], however its frequency varied markedly in different series from 1.7% to 18.7% in six series[2,85]. Recently, the frequency of carcinoid-syndrome in the US SEER database(2000–2011) was assessed in patients >65 yrs. of age[•55,]. Of 9512 eligible NET patients,19% had carcinoid-syndrome and the proportion increased 72 % from 2000 to 2011(11% to 19%). This increase in carcinoid frequency mirrors the general increase in frequency of NETs in the SEER database [86], with a 6.4-fold age-adjusted increase from 1973 to 2012(1.09 to 6.98 per 100000), with the highest increases in the lung(1.49/100000), GI-tract(3.56/100000) and unknown primary sites(0.84/100000). In the recent SEER database analysis[86] patients with carcinoid-syndrome were more likely female(p=0.003), non-Hispanic white race, and have advanced tumor stage, lower grade and the tumor location had a significant effect(p<0.0001)[•55,]. Historically, it has been well established that the frequency of carcinoid-syndrome varies markedly in carcinoids of different locations[2,84,87]. In older studies, the carcinoid-syndrome was uncommon in patients with duodenal, rectal, CNS, gastric(type 1), colonic or appendiceal carcinoids(<1%), whereas it was more than 8-fold more frequent in carcinoids of other areas of the small intestine, pulmonary tract, pancreas, Type 3 gastric carcinoids and Meckel's diverticulum[2,84,87]. This resulted in midgut carcinoids accounting for a mean of 72% of carcinoid-syndrome cases(11 series, range 52–100%), foregut NETs(stomach, duodenal, lung, pancreas) for 9.1%(range(0–33%), hindgut(colon, rectum) for 2.9%(range-0–8%) and an unknown primary site for 14.3%(range-0–26)[2]. In the recent study of the SEER database[•55,], similar data was obtained with relative frequency of small intestine(40%)>respiratory system(13%)>colon/rectum(10%)> cecum/appendix(2–5%). The molecular basis for this marked heterogeneity in the occurrence of carcinoid-syndrome with carcinoids in different tissues is at present unknown.

Serotonin production by pancreatic NETs(pNETs) is receiving increased attention[88,89,•90] and a recent study investigated this in detail in 255 patients with pNETs[57]. In this study[57], 8 % of the patients demonstrated serotonin secreting pNETs, which is higher than the 1–4% generally reported in the literature, however only 0.8% of the patients had carcinoid-syndrome[57]. Those with serotonin overproduction generally had high plasma chromogranin A levels(CgA), ENETs stage 1V disease, and serotonin was a negative prognostic factor on univariate analysis, but not on multivariate analysis[57]. These results are similar to another study[89] which reported pancreatic serotonin-producing NETs are more frequently malignant and more aggressive than typical NF-pNETs.

Carcinoid-syndrome: clinical presentation

Classically, as well as in recent studies, the carcinoid-syndrome is characterized by the presence during the disease at some time of diarrhea(mean 78% [range-58-100%-12 series]), cutaneous flushing(mean 78% [range-45-96%-12 series]), wheezing/asthma-like

symptoms(mean 12% [range-3-18%-11 series]) and pellagra-like skin lesions with hyperkeratosis and pigmentation(1%)[2,25,•58,84,85,87,91].

Cardiac manifestations(carcinoid heart disease)(CHD) occurs in a mean of 40%(14 series), however it has a wide range in the various series both in the past and in present series(range-11–70)[2,•58, •74,75–77,84,85,87,91,93]. In a number of recent series the frequency of CHD is lower at <20%, a decrease that coincides with widespread use of somatostatin analogues, however, at present there is no clear evidence that their use, either reverses established CHD or prevents it in humans, even though it does in an animal model of carcinoid-syndrome[2,•58,91,92,94–97]. In various series(n=14), the relative order of CHD abnormalities are: tricuspid regurgitation(90–100%)>tricuspid stenosis(40–59%)>pulmonary regurgitation(50–81%)>pulmonary stenosis(25–59%)>mitral regurgitation(40–43%]. At diagnosis in various series 27–43% of the patients with CHD have New York Heart Association Class I, Class II in 30–40%, Class III in13–31% and Class IV in 3–12%[91,94,98,99].

Uncommonly reported in the past in carcinoid-syndrome, as well as in recent studies, are rheumatoid arthritis, arthralgia, ophthalmic flushing leading to vessel occlusion and a variety of problems related to increased fibrosis[•58,61,84,85,87]. These include increased intestinal/mesenteric vessel area fibrosis, occurring especially in patients with small intestinal carcinoids, present in up to 75%[2,•58,61]. Other uncommon problems due to fibrosis include retroperitoneal fibrosis leading to ureteral obstruction, Peyronie's disease of the penis, pleural and pulmonary fibrosis[2,61,84,85,87].

Recently, the occurrence of cognitive changes in patients with carcinoid-syndrome is being increasingly reported[59,60,100,101]. These studies report decreased mental processing speed, visual memory and verbal recall, cognitive efficiency, aggressive behavior and language problems[59,60,100,101]. At present, it is unclear the frequency of these CNS symptoms or their exact effect on quality of life in patients with carcinoid-syndrome.

Carcinoid-syndrome: pathogenesis

Many studies support the conclusion that the carcinoid-syndrome occurs only when sufficient amounts of the tumor-released hormonal/bioactive products reach the systemic circulation, as they are inactivated if released into the portal circulation[2,•58,•74,•76,85,87,90,94,96,97,102]. In 87–100%(mean-96.5%) of patients in both older, as well as recent series, this is accomplished by the presence of liver metastases, which circumvents the hepatic inactivation of the bioactive peptides/amines[2,•74, •76,85,87,90,91,102,103]. However, it is important to remember that in in a mean of 5% of patients in different series, but in up to 13% in a recent series[91], the carcinoid-syndrome can develop in patients without hepatic metastases[2,•58,84,103] This occurs particularly with NET-primaries in the ovary[2,104–106], testis[2,107–109], lung/bronchi[2,25,110,111], pancreas[2,90,112] or occasionally, with GI-NETs with large retroperitoneal metastases[103,113–116].

Numerous potential mediators of the clinical features of carcinoid-syndrome have been reported, including overproduction of serotonin(98–100% in most series), which is most

frequently used to assess for the presence of carcinoid-syndrome, and characteristically assessed by determining elevated quantities of the serotonin-breakdown product, 5-HIAA(5-hydroxy-indole acetic acid) in the urine[2,25,•58,72,84]. In addition, excess release of the serotonin precursor,5-HTP(5-hydroxytryptophan), prostaglandins, tachykinins(substance P and neurokinin A), GI peptides, other kinins(bradykinin), and rarely histamine(in foregut carcinoids), have all been reported and to possibly contribute to the different symptoms of carcinoid-syndrome[2,25,•58,72,117].

The exact role of the different potential mediators in causing the noncardiac clinical symptoms of carcinoid-syndrome is unclear. Serotonin is generally thought to be important in mediating the diarrhea of carcinoid-syndrome, because the effects of serotonin on gut motility and secretion, as well as the finding that serotonin receptor antagonists relieve the diarrhea in many patients and in animal models of carcinoid-syndrome, chronic serotonin administration caused diarrhea[2,•58,97,118]. In contrast, serotonin antagonists have little effect on the flushing and its exact mediators remain unclear, except in the case of the flushing seen with some foregut carcinoids which is mediated by histamine[2,25,•58,93,98]. Serotonin is an important mediator of the fibrosis, both cardiac(see below) and noncardiac, likely via activation of 5-HT_{2B} receptors[2,•58,61].

Recent data from the studies of the effect of telotristat in patients with carcinoid-syndrome are providing some important insights into the pathogenesis of some of the noncardiac clinical symptoms. Telostristat ethyl is a tryptophan hydroxylase(TPH) inhibitor, the rate limiting step in the synthesis of serotonin, which acts peripherally, because it does not penetrate the blood brain barrier, and has recently been approved for the treatment of diarrhea in patients with carcinoid-syndrome(See treatment section below)[31, •32,33, •34,35,119,•120]. Results were recently reported from the TELESTAR study(a double-blind randomized, placebo controlled, phase 3 study) of the efficacy/safety of Telostristat in 135 patients with carcinoid-syndrome with diarrhea not adequately controlled by somatostatin analogues[31]. Telotristat significantly reduced the frequency of the diarrhea and the urinary 5-HIAA levels, but had no significant effect on the flushing, supporting the importance of serotonin overproduction in the pathogenesis of the diarrhea, but not for flushing, at least in most patients[31]. In some patients, the serotonin may play a role in flushing, because in a multicenter, single-arm study of the efficacy of telotristat in 15 patients with carcinoid-syndrome, a significant decrease in flushing was seen($p=0.04$)[33].

Pellagra been reported in patients with carcinoid-syndrome because tryptophan is a precursor for both niacin and serotonin and the large increase in serotonin synthesis may lead to niacin depletion causing pellagra[•121,122]. Although pellagra is uncommon in carcinoid-syndrome [usually<1%, but up to 3% in one study[122]], niacin deficiency is not uncommon, occurring 10/36(28%) of patients in one study[122]. In a recent study[•121]) of 42 patients with carcinoid-syndrome with tryptophan deficiency and/or pellagra treated with niacin, the pre-supplementation urinary levels of N1-NN(N1-methylnicotinamide, a urinary niacin metabolite, was initially lower than control values in treated patients and below normal in 45% of the patients. Furthermore, niacin supplementation[•121] normalized the niacin levels.

CHD is due to endocardial fibrosis which is diffuse involving both valves and cordae, is primarily right-sided, although left-sided lesions occur in 5–30% in both recent and older series[2,•74,91,98]. This differential right-sided occurrence is thought due to inactivation of the bioactive tumor products by the lung: an assertion which is supported by the more frequent occurrence of left-sided lesions in patients with intra-cardiac shunting such as with a patent foramen ovale[•74,98]. The released tumor vasoactive products stimulate myofibroblasts proliferation, local deposition of extracellular matrix(collagen, elastin, mxyoid ground substance)/fiber, with the resultant formation of plaques in the endocardium and valves resulting in both retraction and thickening[•74,93,123]. Patients with CHD have higher urinary excretion rates of 5-HIAA and higher plasma levels of Neurokinin A, Substance P, Atrial natriuretic factor, Pro-brain natriuretic factor, chromogranin A(CGA) than patients without CHD[2,•74,91,94,124,125]. Older, as well as recent studies, support a prominent role for serotonin in the pathogenesis of CHD. CHD lesions develop in animals after long-term administration of serotonin: in animals with a deficiency of the 5-HIAA transporter gene, resulting in impaired inactivation of serotonin: or in animals developing the carcinoid-syndrome after intra-pancreatic injection of BON NET cells which secrete serotonin[93,97,118,126,127–129]. Serotoninergic drugs used in the treatment of obesity, migraine or Parkinson's disease cause cardiac lesions which are indistinguishable from CHD, all of which have high affinity for 5-HT_{2B} receptors which are abundant on human heart valves[•76,91,93,126,130,131]. CHD has been reported to progress despite treatment with somatostatin analogues resulting in marked decreases in serotonin overproduction[91,92,94,96], suggesting that other factors are likely also involved. Other factors proposed include bradykinin, tachykinins(substance Neurokinin A, Neuropeptide K), prostaglandins, Activin A, connective tissue factor and transforming growth factor β. The availability of telotristat may provide important insights into the pathogenesis of CHD. Because it inhibits TPH activity resulting in blockage of the conversion of tryptophan to serotonin peripherally and markedly decreases serotonin overproduction[••31,•34,119], its use should help address the question of the role of the hyperserotonemia in both the generation and progression of CHD and possibly the role of other growth factors[••3]. The only information available so far is a recent abstract[132] on two patients with carcinoid-syndrome who demonstrated no further progression of their valvular heart disease while taking telotristat and the authors suggested that its use may prevent the need for valve surgery in some patients. Only further long-term studies with telotristat will address this issue.

Carcinoid-syndrome and CHD: Diagnosis

The diagnosis of carcinoid syndrome is usually initially suspected when a patient presents with flushing, diarrhea, with or without a known NET. The most frequent initial examination to confirm the diagnosis is assessment of urinary 24 hour 5-HIAA which has a sensitivity of 73–91% [84,87]. with a specificity of 100%, if the appropriate precautions are followed(appropriate diet, avoid known interfering drugs). It is important to remember that 18–88% of carcinoid tumors in different series[2] are reported to having overproduction of serotonin assessed by 5-HIAA, with 12–26% not having the carcinoid-syndrome[2]. A recent example of this recently[56] reported is pancreatic carcinoids in which in series of

255 patients, in 8%(20/255) the NET was serotonin-secreting, however carcinoid-syndrome was only present in 0.8%(2/255).

Recent studies demonstrate that assessment of plasma 5-HIAA can be used instead of the urinary 5-HIAA collection[70,•71,73]. In these studies plasma and/or serum 5-HIAA correlated closely with the urinary 5-HIAA levels($p \leq 0.0001$): it has a similar sensitivity to urinary 5-HIAA(91–92%): was not affect by meals or time of day: had the advantage of allowing a single determination rather than a 24-hour collection: but had the disadvantage that it was affected by renal impairment with glomerular filtration rates <60mL/Min[70,•71,73].

It is recommended in most guidelines and expert opinion articles that CHD should be screened for using echocardiography[52,91,98,133]. This point is emphasized by the findings in one study[91], where 57% of the patients with severe CHD on echocardiographic studies were either asymptomatic or had mild cardiac symptoms. Several biomarkers have been proposed to identify and assess the severity of CHD. These include N-terminal pro B-type natriuretic peptide(NT-proBNP), CgA, TGF, FGF(fibroblast growth factor) and 5-HIAA[•76,95,125,134–136]. Increased plasma/urine levels of 5-HIAA are associated with increased risk of CHD and with progression of CHD[•76,92,94–96,125]: identification of increased levels of NT-proBNP is a useful screening test for CHD[•76,134,136] with levels>260 pg/ml) having a sensitivity and specificity of 92% and 91% for CHD in one study[135]: CgA is reported to have high sensitivity for identifying CHD(100%), but a low specificity(30%)[76,136] and activin A is also reported to have high sensitivity for CHD(87%), but a lower specificity(57%)[137].

Carcinoid-syndrome: treatment

Carcinoid-syndrome: treatment: somatostatin analogues—Somatostatin analogues have become the standard initial treatment for controlling the symptoms in carcinoid-syndrome[••3,52,•58,133,138], are used frequently in patients with CHD(discussed separately below) and for controlling the growth of the carcinoid itself in patients with advanced disease[139,•140–142]. In numerous studies the presence of carcinoid-syndrome has been reported to have a detrimental effect on prognosis[•55,76,143]. Because of this and their known antigrowth effects on the tumor per se, it has recently been recommending that somatostatin should be started in patients when the diagnosis of the NET is made and its accompanying carcinoid-syndrome are established[143].

Since the initial studies using short-acting octreotide administration in the 1980s, followed more recently by long-acting preparations of octreotide or lanreotide requiring monthly administration, it has been established that these somatostatin analogues can control many of the noncardiac symptoms(particularly flushing, diarrhea)(in patients with the carcinoid-syndrome[19,20,23,24,26,27,138,144]. In these studies, long-acting octreotide and lanreotide controlled symptoms of diarrhea/flushing in 60–72% and 55–75% of symptomatic patients. In the recent reported ELECT study[••22,], a randomized double-blind study using lanreotide autogel involving 150 patients with carcinoid-syndrome, the long-acting lanreotide preparation decreased the use of rescue octreotide significantly(15%) ($p=0.036$) and the proportion achieving complete/partial symptom relief with lanreotide

autogel treatment was twice as great as patients taking placebo with/of without short-acting octreotide. Patient reported outcome satsifaction with lanreotide autogel treatment in 273 patients with carcinoid-syndrome also was recently reported[24] and was 76% for patients with diarrhea and 73% with flushing.

In all long-term studies a proportion of patients with carcinoid-syndrome(30–76% in many studies) are not controlled by the highest standard doses of lanreotide or octreotide at some time during trament[7,10,19,20,23,24,26,27,37,138,144,145,•146]. In these refractory patients, increasingly, either more frequent dosing of the somatostatin analogue is used or high-dosing at the same time interval to control the extra-cardiac symptoms, and this approach is frequently effective(up to 80%)[••3,7–11,26,29,50,•146]. Recent studies also support the conclusion that pasireotide(SOM230), a somatostatin analogue with high affinity for somatostatin receptor subtypes-sst1,2,3,5 [in contrast to octreotide/lanreotide with high affinity for sst2,5], may be effective in controlling noncardiac symptoms(diarrhea/flushing) in a proportion of octreotide/lanreotide resistant patients with carcinoid symptoms[12,37,147]. In one phase II study[12] in 48 patients with carcinoid-syndrome no longer responsive to octreotide LAR, pasireotide controlled the diarrhea/flushing in 27% of the patients. With pasireotide treatment hyperglycemia developed in higher proportion of patients than seen with octreotide-LAR[145] with hyperglycemia in 28%,16% and 79% in three different studies[12,37,147]. In a study investigating the possible mechanism of the pasireotide induced hyperglycemia in normal volunteers, it was found that pasireotide decreased the incretin response and insulin secretion without affecting peripheral or hepatic insulin sensitivity[148].

Carcinoid-syndrome: treatment: in patients refractory to somatostatin analogues—If dose-escalation of Octreotide-LAR or Lanreotide Autogel is not effective in controlling the noncardiac symptoms of carcinoid-syndrome(primarily diarrhea/flushing), recently, several other approaches have been reported to be effective, although in some cases, only in small numbers of patients[2,••3,••22,24,36,•146,149,•150].

Recent studies report effectiveness if the mTOR inhibitor, everolimus, in controlling symptoms in refractory cases[••3,36,•146,151],(symptom control=70% in one study)[36], like its ability to control various functional-pNET syndromes(insulinoma, etc.)[••3,36,•146]. This occurs within days of everolimus administration and thus is independent of its antiproliferative effects, which have been shown in several large, controlled trials, as well as other studies, for both carcinoids and pNETs[36,••82,152–154].

PRRT(peptide-directed radiotherapy) using ^{177}Lu-Dotatate(with octreotide-LAR) has recently[39] been shown in a double-blind, prospective, randomized study, to markedly prolong progressive-free survival compared to octreotide-LAR alone, in patients with advanced metastatic well-differentiated midgut NETs. In uncontrolled studies and case studies, the effective control of refractory carcinoid-syndrome symptoms(noncardiac) is reported using PRRT with ^{177}Lu-Dotatate or ^{90}Y-Edotreotide in 63–90 % of patients[••3,••22,40, •51,•146,155,156,•157,158]. In most studies the symptomatic responses of the carcinoid-syndrome with PRRT are durable, lasting>6 months, but little data is available for longer periods. The relationship of the time course of the symptomatic response

in patients with the carcinoid-syndrome and the effect on the tumor growth have not been well studied with PRRT and are unclear at present.

Control of symptoms due to carcinoid-syndrome refractory to treatment with somatostatin analogues has also been reported in patients undergoing cytoreductive surgery in 50–90 % of patients[••3,52,53,•146,•150,159] and with the use of ^{131}I-MIBG treatment(metaiodobenzylguanidine) in 40–75% of patients showing clinical improvement[••3,•146,160–163]. After ^{131}I-MIBG treatment, patients frequently require either no somatostatin supplemental treatment or lower doses to control the carcinoid-syndrome with a mean response time of 6–15 mos. and responses lasting up to 39mos[••3,•146,160–163].

Various liver-directed therapies have been reported to be effective at controlling the symptoms of carcinoid-syndrome in somatostatin resistant patients[••3,•146]. These include: radiofrequency ablation(RFA) either performed percutaneously, at laparoscopy or at the time of open surgery resulting in symptomatic control in 70–97%(with or without surgery) with a mean duration of 11–14 mos.[3,•146,164–167]: radioembolization or SIRTs(selective internal radiation therapy) with ^{90}Yttrium(^{90}Y)-labeled microspheres [either ^{90}Y-resin microspheres(SIR-spheres) or ^{90}Y-glass microspheres(Theraspheres)] with symptom control in 50–94 % of patients[••3,45,47,48,168] or after TACE/TAE(trans-arterial chemoembolization/transarterial embolization) with a clinical response rate in most studies of 54–88% % of patients with a mean duration of 13–80 mos. and biochemical response rate of 50–100%[••3,42,43,45,49,•146,169,170]. In the TACE studies generally either cisplatin or doxorubicin was used[45] as the chemotherapeutic agents and more recently drug-eluting beads with doxorubicin or streptozotocin[42,43,45,46,49,170].

One important aspect of the use of radioembolization for control of refractory carcinoid-syndrome in patients with initially unresectable liver metastases is pointed out in recent papers describing the increased difficulty and increased risks associated with subsequent hepatic surgery in these patients post-radioembolization, likely because of the radioembolization induced changes[171,172]

Also, effective in the treatment of the diarrhea in carcinoid-syndrome patients refractory to somatosatin analogue therapy is the recently approved TPH inhibitor, telotristat ethyl(see below), which blocks the synthesis of serotonin peripherally and controls diarrhea in 44% of refractory patients[••3,••31,•146]. This will be discussed in more detail in the next section.

Carcinoid-syndrome: treatment: Telotristat ethyl

As reviewed above, serotonin overproduction is thought to be a key mediator in the pathogenesis of several symptoms of the carcinoid-syndrome. The rate limiting step in serotonin's synthesis is the conversion of tryptophan to 5-hydroxytryptopah(5-HTP) by tryptophan hydroxylase(TPH)[2,•34,119,173]. One of the earliest drugs used to treat carcinoid-syndrome was parachlorophenylanine, an inhibitor of TPH, which was effective at controlling the diarrhea, not the flushing, however because of numerous side-effects, particularly in the CNS(behavioral, insomnia, depression hallucinations, etc.), its usage stopped[119,173,174]. Subsequently, it was found there are two isoforms of TPH, THP2

which occurs in the brain and TPH1, which occurs in peripheral tissues[•34,119]. Telotristat(LX1606) has high affinity for both TPH1 and TPH2, but does not cross the blood brain barrier, so it only acts peripherally[•34,119].

The recently completed TELESTAR study[31][NCT01677910], was a double-blind, placebo-controlled trial Phase-3 study involving 135 patients with carcinoid-syndrome who were refractory to treatment with somatostatin analogues. Patients had to have ≥4 bowel-movements/day and were treated with placebo or telotristat(250 or 500mg taken orally t.i.d) over a 12-week period with an open label 36-week extension. The 250mg and 500mg doses significantly($p<0.001$) reduced bowel-movement(BM) frequency ≥30% for ≥50% of the treatment period in 44% and 42%, respectively, of the patients, with placebo causing a 20% decrease[31]. The decrease in diarrhea was accompanied by a marked decrease in urinary 5-HIAA of ≥30% in 78% of the 250mg treated patients and 87% of the 500mg treated($p<0.001$).

The TELESTAR results were consistent[32] with results of another Phase-3 study(TELECAST-study)(NCT02026063) published in abstract form only at present[•32,175] and two phase-2 studies[NCT01104415[33] and NCT00853047[35]]. The TELECAST study[•32,175] included 75 patients and was a double-blind study(placebo,250 and 500mg telotristat dosing taken orally t.i.d) similar in design to the TELESTAR-study, but with patients refractory to somatostatin analogues with ≥1 bowel-movement per day(BMs/day). Both the 250mg($p<0.001$) and the 500mg($p<0.001$) decreased urinary 5-HIAA(56% and 90%, respectively), and both telotristat doses decreased bowel-movement frequency significantly($p<0.001$)[•32,175]. The two Phase-2 studies NCT01104415[33] and NCT00853047[35] were performed in Germany/United Kingdom and the U.S., respectively. In the NCT01104415[33] Phase-2 study patients(15 carcinoid-syndrome patients enrolled) had to have ≥4 BMs/day with or without somatostatin analogue treatment and received oral telotristat 150mg t.i.d for 2 weeks. If no toxicity was seen, doses could be increased to 250mg t.i.d, then 350 t.i.d for 2 weeks and finally to 500tid for 2weeks and then continued the highest dose tolerated for an additional 4 weeks(total-12weeks)[33]. All patients had a decrease in BMs frequency(40%≥50%) and urinary 5-HIAA excretion decreased by 74%[33]. In the 00853047 Phase 2 study[35] patients with octreotide treatment refractory carcinoid-syndrome with ≥4 BMs/day were randomized to 28-day treatment with placebo(n=5) telotristat at 150(n=3),250(n=3),350(n=3) or 500mg t.i.d(n=9). At least a ≥30% reduction in BMs/day was seen in 28% of the telotristat treated patients and in none of the placebo treated[35]. In addition,75% of the telotristat treated and only 20% of the placebo treated, had at least some decrease in BM frequency for 14 of the 28-day trial. Urinary 5-HIAA normalized in 56% of the telotristat-treated and none of the placebo-treated[35].

A Phase-3 TELEPATH(NCT02026063) trial in patients with carcinoid-syndrome who completed either a Phase2/3 trial is still ongoing. The primary aim of this study is to evaluate long-term safety with a secondary study involving quality of life through week 84[32].

In the safety data analysis from the TELSTAR and TELECAST-studies, similar numbers of placebo-treated or telotristat patients at the different doses had ≥1 adverse event and similar

numbers discontinued the study because of side-effects[32]. In the TELESTAR-study[31], telotristat at the 250mg dose caused an increase in alanine transaminase in 2.2%, at the 500mg dose in 6.7%, where 0% of the -treated showed increases. Nausea occurred in 31.1% of the patients treated with the 500mg telotristat dose,13.3% of these treated with the 250mg dose and 11.1% of placebo-treated[31]. Lastly, the rate of depression was increased in patients treated with the 500mg telotristat dose at 15.6%, whereas no increase was seen in patients treated with the 250mg dose compared to placebo(6.7%)[31]. Telotristat is reported not to cross the blood-brain barrier, however the increased occurrence of depression on the higher dose of telotristat in the TELESTAR study will be a finding that needs further evaluation and will likely be clarified in the long-term safety data acquired from the ongoing TELEPATH study.

Carcinoid-syndrome: treatment: Carcinoid heart Disease(CHD)

One of the most important steps in the treatment of CHD is to first established its presence. In various studies, in up to 37% of the patients with CHD and carcinoid-syndrome, the CHD is asymptomatic[91], and this can occur even in up to 57% of patients with advanced CHD[91]. At present, there is a mean delay in diagnosis of CHD on 1.5 years from the time of detection of CHD[94] and CHD is associated with a poor prognosis[93,134,176]. Therefore, CHD's timely detection would allow treatment of early cases to be started which may help progression[91,96], and treatment of advanced cases to be carried out[•76,99,176]. Timely surgical treatment of advanced cases of CHD has been shown to markedly improve survival[92] and increased recognition and treatment of CHD has resulted in an improvement in 5-yr survival from <30% in the 1980s to 55% at present[99,133]. Therefore, it is essential to screen patients with carcinoid-syndrome for CHD and it is generally recommended that this be performed with echocardiography[•76,93,177,178]. This is recommended in most recent guidelines and reviews because of its sensitivity and because the clinical correlates to suggest the presence of CHD are generally poor[•76,91,178].

Several recent reviews have covered numerous aspects of the most current advances and changes in the recognition and management of CHD[•74,75,•76,77–80]. A few of the most important points will be briefly reviewed here.

Whereas all guidelines/expert opinion recommend echocardiography as the imaging study for identifying CHD[•76,77,99,179], a recent study demonstrates there is considerable heterogeneity in UK/Ireland NET centers on aspects of screening for CHD[180]. In this report[180], 28 NET centers treating 5500 NET patients in UK/Ireland were sent a questionnaire evaluating aspects of CHD screening and management in NET patients. It was found that 11% of centers screen all NETs patients for CHD,14% only patients with midgut NETs, 32% all patients with liver metastases and/or carcinoid-syndrome, and 43% only patients with carcinoid-syndrome or elevated urinary/serum/plasma 5-HIAA[125]. In this survey[125] 80% of the NET centers used screening with echocardiography with 24% using it on the initial presentation, 28% used it at periodic unspecified intervals, 32% annually and 12% less than annually. One-half the centers utilized markers(5-HIAA, CgA) or more commonly NT-proBNP at varying intervals to screen for CHD[125].

Recent studies have reported the potential additive value of color Doppler analysis[178],3-D echocardiographic analysis[178,181], cardiac MRI[•74,178,181] and proposed various echocardiographic scoring systems for assessing progression in CHD[•76,182]. However, the clinical relevance of these scoring systems and which patients with which CHD abnormalities they are best used in, is uncertain at present[•76,183]. Also reported are studies of various possible plasma markers for identifying CHD including TGF-β (transforming growth factor-β), fibroblast growth factor(FGF), Activin A, chromogranin A(CgA), chromogranin B(CgA), C-reactive protein(CRP), Neurokinin A(NKA), 5-HIAA, N-terminal pro Brain Natriuretic Peptide, and atrial natriuretic peptide(ANP)and urinary markers(5-HIAA)[77,125,134,135,137,184]. In these studies, high levels of urinary 5-HIAA[•74,•76,134,137] and plasma 5-HIAA[125], NT-proBNP[20,135,184], ANF[134], NKA[180], CRP[137], activin A[137], CgB[125] or CgA[137,184] were associated with the presence of CHD. In a comparative study[125] of serum/plasma levels of CgA, CgB,5-HIAA, NKA and NT-proBNP, the NT-proBNP best correlated with the presence of CHD with a 200 ng/L cutoff having a sensitivity of 74% and specificity of 73. NANETs guidelines suggest NT-proBNP levels should be considered in patients with carcinoid-syndrome for screening to select those for further echocardiographic studies[77]. Plasma levels of connective tissue growth factor(CCN2) inversely correlated with the presence of right ventricular dysfunction and valvular regurgitation in NET patients[185].

Predictors of progressive disease in CHD have been assessed in several studies. In various serial studies CHD progression was reported in 9–35%[•76,92,95,96]. In CHD progressors in various studies[92,95,96] higher baseline level of serum NT-proBNP[95] and plasma/urinary 5-HIAA were associated with progression[•74,92,95,96,137]. Every 100nmol/L increase in plasma HIAA was associated with a 5% greater risk of disease progression and 7% greater risk of death[95]. Other prognostic factors reported are receiving chemotherapy[92], greater than 3 flushing attacks/day[96], high tumor grade[95], echocardiographic score[95], prior tumor resection[95], and worsening of carcinoid-syndrome symptoms[95,96].

Treatment for CHD requires initially the use of pharmacotherapy of heart failure(primarily with diuretics) and control of carcinoid symptoms(initially with somatostatin analogues, then other therapies in refractory cases outline earlier)[2,•76]. Although at present there is no evidence that medical treatment of the carcinoid-syndrome with somatostatin analogues affects either the development or progression of CHD[•74], several changes are occurring which may change this conclusion. First, somatostatin analogues are now being used much earlier in patients with NETs, including asymptomatic patients or patients with minimal carcinoid symptoms, because of the recent studies showing their anti-proliferative effects on tumor growth[139,•140,141]. Second, with the availability of other methods to control the carcinoid-syndrome(covered above in treatment of refractory cases), a larger number of patients will have their carcinoid-syndrome controlled with reduced serotonin-overproduction. Thirdly, with the availability of telotristat, which has a drastically ability to reduce serotonin overproduction[••31,33,35,175], coupled with the fact that many studies demonstrate both the development and progression of CHD correlate with high levels of serotonin overproduction, therapy with telotristat could influence CHD, although at present this is unproven.

Some evidence supports the conclusion that resection of the tumor may retard the progression of CHD or prevent its development[99,186]. In a study in which hepatic resection was performed in 31 patients with CHD with metastatic disease to the liver, in which at least 90% of the tumor was thought resectable, the 5-yr survival was significantly higher than those not undergoing resection. Furthermore, on multivariate analysis the surgical resection was strongly associated with survival($p=0.003$) and was independently associated with a decreased risk of cardiac progression($p=0.03$). Whether the recently demonstrated antiproliferative activity of somatostatin analogues[139–141], the mTor inhibitor, everolimus[••82,153], or PRRT with ^{177}Lu-Dotatate[39] will have a similar effect, is at present is unknown.

Valvular surgery remains the definitive treatment for CHD-related symptoms and has been shown to result in marked symptomatic improvement and survival[•76,99,187]. Several recent reports have covered various advances in the management of CHD-symptomatic CHD. These include are number of different areas. There are promising results of the use of percutaneous balloon valuloplasty to treat stenotic pulmonary or tricuspid valves in a small number of patients with CHD who are not surgical candidates[•188,189,190]. Whereas this approach can result in rapid symptomatic improvement, in some patients there is a rapid relapse of symptoms which may limit its usefulness[93,99,183,•188,189,190]. There is controversy about the type of valve prosthesis to insert in patients with CHD[99,183]. Biological prosthetic valve replacement has the advantage of not requiring life-long anticoagulation, making subsequent surgery, or other procedures easier to perform[99,187]. However, biological prosthetic valve degeneration with valve failure is reported in <6 mos. in some patients after surgical implantation, and may be related to the circulating bioactive secretion products from the carcinoid tumor originally causing CHD[•76,99,183]. However, the use of mechanical prostheses, which were previous generally recommended, are not without problems in that they require patient anticoagulation in many cases in patients with frequent increased risk of bleeding from hepatic dysfunction or of valve thrombosis[99,183]. Another contentious area of treatment of CHD is the issue of the indications for valve surgery: an area where there is no overall agreement[•76,80,99]. Previously patients with progressive disease refractory to medical treatment were considered suitable candidates, however they had a high risk of death and perioperative mortality of 30–60%[98,99]. Recently, it has been increasing recommended that patients with CHD be referred earlier for surgery, even patients with advanced CHD, but without symptoms, or patients with symptoms of right heart failure, progressive right ventricular dilation or decline in right ventricular function, or requiring hepatic surgery[99,179]. Perioperative mortality rates have improved in recent years to 5–18%[78,99,176,191] and long term survival has improved with 5-yr survival rates of up to 35–43%[79,99,176,191], whereas in the past without valve surgery only 10% of NYHA Class II or IV survived 2 years[191], supporting this recommendation.

Carcinoid-syndrome: Carcinoid Crisis

A carcinoid crisis is one of the most serious complications of the carcinoid-syndrome[2,176,192–194]. Carcinoid crises are often precipitated by various procedures(surgery, anesthesia, endoscopy, chemotherapy, PRRT, radiological procedures

[such as biopsies, embolization], but can also be precipitated by stress or abdominal palpation of the tumor area during examination of the patient[2,192–195]. The symptoms/signs characteristically include marked changes in blood pressure(usually hypotension, frequently with shock: however, hypertension can occur also[196]), CNS symptoms(stupor, confusion), flushing, diarrhea, bronchospasm, hyperthermia and cardiac arrhythmias[2,192–194,197,198]. This is serious complication in carcinoid-syndrome patients and needs to be treated, because it can result in death[2,193,194,197,199,200]. Several controversies in its treatment have recently become apparent.

Historically, carcinoid crises was treated by parenteral administration of somatostatin analogues and this was accepted as giving both effective prevention and therapeutic treatment, and this approach was included in several recent guidelines[52,•76,•150,192–194,201,202]. Controversies now exist as to whether somatostatin analogues are adequately preventing carcinoid crises[203,203,204,•205,206] and if so, what is the proper dosage and timing of the dose[200,202,203,•205]. Based on these concerns, some groups have proposed revised guidelines for prevention of carcinoid crisis for procedures and surgery involving high dose infusion of octreotide[200,•205], although, this approach has been questioned based on methodical issues, in one systematic analysis of these studies[202].

Conclusions

In the last few years there have been many advances in the management of NETs, including both nonfunctional NETs and NETs causing functional syndromes such as the carcinoid-syndrome, which is the most frequent. There have been advances in many aspects of the carcinoid-syndrome all of which are reviewed in this article, including an increased understanding of its epidemiology demonstrating it’s increasing frequency: new methods to establish its diagnosis: an increased understanding of its natural history and pathogenesis and important new approaches to its treatment. The later include both new approaches initially as well as new approaches to treat the symptoms of patients with carcinoid-syndrome refractory to somatostatin analogues. Also, there is an increased understanding of the pathogenesis of carcinoid heart disease and its management, including the possibility that some of the newer drugs many either prevent its development or slow its progression. These advances have not occurred without controversies, and these are also briefly reviewed here.

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KEY POINTS

- There have been advances in all aspects of the carcinoid-syndrome over the last few years.
- Recent studies have shown it is increasing in frequency, and new insights into the pathogenesis of various clinical manifestations of the carcinoid-syndrome.
- Telotristat, a tryptophan hydroxylase inhibitor, inhibits serotonin overproduction in carcinoid-syndrome, and controls diarrhea in phase-3 controlled trials
- Several different approaches are now described to treat symptoms of carcinoid-syndrome in patients refractory to somatostatin analogues and understanding/ management of carcinoid-heart disease has progressed with improved treatment results.
- These advances have generated a number of controversies and new unanswered questions.