Metastatic Carcinoid Tumors: A Clinical Review

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the epidemiology of carcinoid tumors and the survival rates observed in patients with different stages of disease.
2. Discuss the diagnostic modalities available for assessing carcinoid tumors and be able to use the results of these studies to choose a treatment option.
3. Summarize the current therapeutic options for the treatment of carcinoid tumors.
4. Identify the importance of carcinoid-related heart disease (CHD) on prognosis in patients with carcinoid tumors.

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ABSTRACT

Carcinoid tumors are neuroendocrine tumors derived from enterochromaffin cells, which are widely distributed in the body. They can originate from any location in the body, but they are traditionally described as originating from the foregut, midgut, and hindgut. Although the overall incidence of carcinoid tumors appears to have increased in the past decades, the prognosis for patients with metastatic carcinoid tumors has improved during the last decade. Due to longer survival times, complications, such as carcinoid heart disease, and new metastatic patterns, like skin and bone metastases, may become more important features of carcinoid disease. Therapy focused on these complications should be part of the management. Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in better quality of life and longer survival times. The increasing number of therapeutic options and diagnostic procedures requires a multidisciplinary approach, with decisions made in multidisciplinary meetings focused on "tailor-made" therapy based on patients' specific conditions. Because carcinoid tumors are uncommon, effort should be made to treat these patients in specialized centers and for these centers to join together in multicenter studies. *The Oncologist* 2005;10:123-131

INTRODUCTION AND EPIDEMIOLOGY

Carcinoid tumors were first described in 1888 by Lubarsch, who found multiple tumors in the distal ileum of two patients at autopsy. The term "karzinoide tumoren" was first used in 1907 by Oberndorfer to describe a similar tumor that was morphologically distinct and less aggressive in behavior than classical adenocarcinomas [1]. Carcinoid tumors are neuroendocrine tumors derived from enterochromaffin or

Kulchitsky cells, which are widely distributed in the body. For this reason, they may be found at any location in the body, but they are traditionally described as originating from the foregut, midgut, and hindgut.

The annual incidence of carcinoid tumors is around two cases per 100,000, and it varies with gender, age, and race. However, in autopsies, the incidental finding of these tumors is much higher (up to 0.5%–1%), with the main location being the small intestine [2]. The overall incidence of carcinoid tumors appears to have increased in the past decades [3], possibly as a result of changes in the detection rate [4]. In age-specific incidence rates, a peak between 15 and 25 years and another peak between 65 and 75 years can be found. Under the age of 50, the incidence is approximately twice as high in females as it is in males. At older ages, a male predominance is observed, with a rate double that of women [4, 5]. For all sites, age-adjusted incidence rates are higher in males of African descent (4.48 cases per 100,000 [3]). The sites most often affected by carcinoid tumors are the gastrointestinal tract (about 65%) followed by the bronchopulmonary tract (about 25%). In about 10% of cases, the primary tumor site remains unknown. Presentation with distant metastases is found in 22% of cases, half of which have unknown primaries.

The overall 5-year survival rate for all carcinoid tumors (regardless of site or stage) ranges from 70%–80% [3, 5]. As might be expected, stage of disease influences the prognosis significantly, with the best 5-year survival rate in localized disease (93%) and a poor 5-year survival rate in distant metastatic disease (20%–30%). The best overall 5-year survival rates are observed in patients with appendiceal and lung carcinoid tumors (95% and 80%, respectively) due to a low rate of invasive growth or metastatic spread. Survival has improved over the last decades [3, 5, 6]. In a study by Quaedvlieg et al. [5], the introduction of octreotide (Sandostatin®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) therapy was suggested to be a factor in the improvement of survival in patients with metastatic disease.

HEREDITARY PREDISPOSITION

Information on risk factors in carcinoid tumors is scarce, and most carcinoid tumors are assumed to be sporadic. In a minority of patients with carcinoid tumors, the multiple endocrine neoplasia type 1 (*MEN-1*) gene has been implicated. This is an autosomal dominantly inherited disorder, with the *MEN-1* gene localized to chromosome 11 (11q13). The classical syndrome includes neoplasia of the parathyroid glands, pancreas, and anterior pituitary and neuroendocrine tumors of the lungs, thymus, and stomach (foregut) [7]. A family history of carcinoid tumors is reported in <1% of patients, and some case reports have been published on this subject [8]. However, the relative risk of developing a carcinoid tumor for an individual with one affected first-degree relative is 3.6 (95% confidence interval [CI], 3.3–4.1), and with two affected offspring, the relative rise is >12 (95% CI, 3.2–27.4) [4, 9]. A study performed in familial pulmonary carcinoid tumors not associated with *MEN-1*, did not reveal a specific genetic disorder [10], although lung carcinoids were more prone to have deletions on chromosome 11q. In sporadic midgut carcinoids, a high frequency of deletions on chromosome 18 is described [11]. These findings might indicate different pathways in the development of carcinoid tumors from the foregut and midgut [12].

HISTOLOGY AND CLASSIFICATION

In the last decades, several classification systems for endocrine tumors have been applied. In 1980, the World Health Organization classification of endocrine tumors applied the term "carcinoid" to all tumors of the diffuse neuroendocrine system, excluding islet cell tumors, medullary carcinoma of the thyroid, paraganglioma, small cell lung cancer, and Merkel cell tumors of the skin. The subdivision of carcinoid tumors was made on the basis of various silver and other staining techniques. In the following years, this classification system became outdated due to the development of more detailed immunohistochemical testing methods and a growing demand for a classification focused on prognostic histological features. Probably the most useful classification to predict prognosis of neuroendocrine tumors originating from the gastrointestinal tract is the revised classification of neuroendocrine tumors of the lung, pancreas, and gut by Capella et al. [13]. In this classification system, tumors are graded as: benign, low-grade malignant, and high-grade malignant. The criteria used in this subdivision are histological differentiation, tumor size, angioinvasion, and infiltrative growth. These are combined with the primary tumor site and production of hormones.

Histological features related to prognosis in pulmonary neuroendocrine tumors are described in a study by Travis et al. [14]. A combination of morphology, mitotic index, and necrosis proved to be useful in the prediction of prognosis. An attempt to improve the prognostic power of the classification system was made by Van Eeden et al. [15], who investigated whether a combination of both systems resulted in a fine-tuning of the prediction of prognosis of midgut tumors and unknown primaries. Subdivision of these low-grade tumors appeared to be of less value than this subdivision in neuroendocrine tumors of the lung.

PATHOPHYSIOLOGY AND SEROTONIN METABOLISM

Depending on their site of origin, carcinoid tumors can have the ability to secrete vasoactive peptides. Serotonin

(5-hydroxytryptamine [5-HT]) production is the most prominent, especially in midgut tumors. However, 5-hydroxytryptophan (5-HTP), bradykinins, tachykinins, histamine, substance P, adrenocorticotropic hormone, and several other peptides are also reported to be produced by carcinoids.

Under normal conditions, about 99% of dietary tryptophan is metabolized by the oxidative pathway into nicotinic acid, and <1% is converted into 5-HTP. In carcinoid tumors, a disequilibrium of tryptophan metabolism results in 5-hydroxylation of most of the tryptophan, with the production of large quantities of 5-HTP, 5-HT, and 5-hydroxyindolacetic acid (5-HIAA) [16]. If there is a deficiency of aromatic amino acid decarboxylase in carcinoid tumor cells, conversion of 5-HTP into serotonin will not occur, and the tumors excrete 5-HTP instead of serotonin [17]. Due to this shift, a reduction in nicotinic acid pools can cause pellagra in carcinoid patients [18]. Urinary 5-HIAA, the breakdown product of serotonin, is still an important marker for carcinoid tumors (Fig. 1).

CLINICAL PRESENTATION AND COMPLICATIONS

Carcinoid tumors are relatively slow growing, and even in the presence of metastatic disease, patients can survive for several years. Unless secretory products are directly released into the systemic circulation, systemic signs and symptoms are usually not present. Paracrine secretion of hormonal products in the intestine can cause diarrhea. If there is a release of vasoactive peptides in the systemic circulation (in the case of liver metastases or, e.g., bronchus carcinoid tumors), patients often present with the characteristic symptoms of the carcinoid syndrome, such as diarrhea, flushing, and, less frequently, wheezing. Overproduction of serotonin seems to cause the complaint of diarrhea [19, 20]. The correlation between serotonin production and symptoms of flushes is not convincing, and other hormones like tachykinins are probably of importance in the pathogenesis of this symptom [21, 22]. The cause of wheezing is less clear. It has been suggested that the release of histamine and serotonin could play a role in this symptom, but clear evidence cannot be found in literature.

Carcinoid heart disease (CHD) is a late complication and occurs in 20%–70% of patients with metastatic carcinoid tumors [23, 24]. In many patients, the cause of death is attributed directly to cardiac disease [25]. The pathogenesis of carcinoid heart lesions has not yet been fully elucidated, but serotonin plays an important role. This is supported by the finding of similar valve lesions in patients using appetite suppressants, such as fenfluramine or dexfenfluramine, and antimigraine drugs, such as ergotamin and methysergide, agents which all act via the serotonin pathway [26].

In several studies, urinary 5-HIAA excretion, which is indicative for the amount of serotonin production, was significantly higher in patients with CHD than in those without CHD [23, 24, 27]. Not only a high serotonin level, but also the duration of exposure to serotonin, is important in the development of CHD [27].

Carcinoid crisis with severe flushes and diarrhea leading to dehydration, hypotension, and arrhythmias, along with unconsciousness, is a potential life-threatening complication. It may be provoked by anesthetic administration during invasive procedures and is probably caused by an excessive release of vasoactive peptides into the circulation. Therefore,
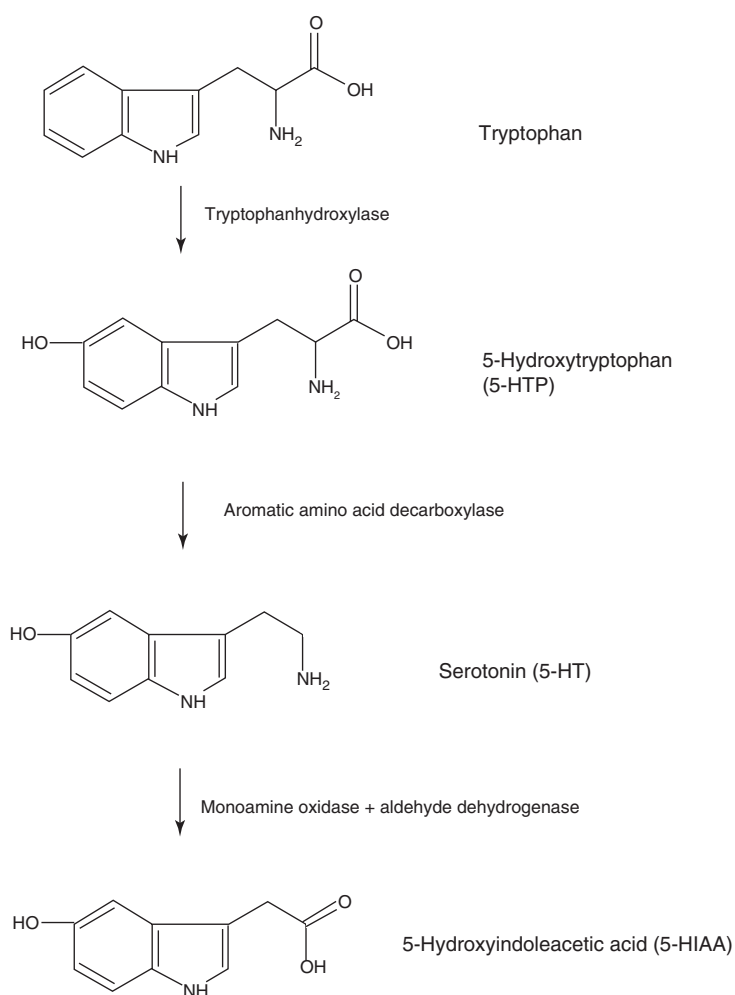

Figure 1. Serotonin metabolism.

it is important that prophylactic measures (such as continuous i.v. octreotide infusion and extra hydration started simultaneously with the intervention) are taken during these procedures to prevent a carcinoid crisis.

In a substantial number of patients, the primary tumor remains unknown despite extensive diagnostic investigations. However, primary tumors in the small bowel can cause complications such as bowel obstruction or fibrosis with shrinkage of the mesentery during follow-up. Due to mesenterial fibrosis, patients can suffer from disabling abdominal pain with malnutrition and kinking of the bowel. Additionally, fibrosis can lead to intestinal ischemia resulting in necrosis and perforation of the bowel wall [28, 29].

Metastases to the skin seem to be a late manifestation of advanced disease, but data in the literature are scant and limited to single case reports only [30]. These metastases may present as painless subcutaneous nodules [30], but sometimes they are extremely painful [31]. The pathogenesis of the severe pain encountered in these often tiny metastatic deposits remains difficult, as neural involvement is not a consistent finding. Pain can be difficult to manage with analgesics, but local excision has been demonstrated to provide satisfactory long-term palliation [31].

The incidence of skeletal metastases in neuroendocrine tumors has been reported to be approximately 10% [32, 33]. Although bone metastases arise more often from bronchial or hindgut primaries than from midgut primary carcinoid tumors, recent studies show no preferential primary site [32, 33]. The axial skeleton is the most commonly affected site [32]. Bone scintigraphy is the most sensitive nuclear imaging technique to detect bone metastases in carcinoid disease and is superior to ^{111}In-pentetreotide (OctreoScan®; Mallinckrodt Inc.; Hazelwood, MO) and ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy [32, 33]. Pain is the main symptom of bone metastases, and radiotherapy provides satisfactory long-term palliation in the majority of patients.

DIAGNOSIS

Pathology

In most patients, the diagnosis is based on tissue examination, usually of a biopsy from a liver metastasis. However, in some patients, attempts to collect histologic material can fail, and in these cases, diagnosis can be based on symptoms combined with radiologic and scintigraphic findings. The biopsy material should be examined by a pathologist familiar with the carcinoid diagnosis to prevent confusion with an adenocarcinoma with neuroendocrine markers. Depending on the presence of necrosis and/or mitosis, tumors can be graded as low-grade malignant or high-grade malignant, which is useful in the prediction of prognosis.

Tumor Markers

Urinary 5-HIAA, the breakdown product of serotonin, has been the gold standard for diagnosis and follow-up of carcinoid patients for many years. The specificity of this determination is almost 100%, but the sensitivity is reported to be much lower (35%) [34]. Urinary 5-HIAA levels can be influenced by food (e.g., bananas, avocados, pineapple, and walnuts) consumption and medication use [35].

The platelet serotonin level is a more sensitive marker for the detection of small amounts of serotonin. However, in cases with a high rate of serotonin excretion, serotonin in platelets reaches a maximum and can no longer be used for quantitative determination and, hence, evaluation during follow-up [36].

Chromogranin A (CgA) is an acidic, hydrophilic protein of 49 kDa present in the chromaffin granules of neuroendocrine cells. In contrast to urinary 5-HIAA and platelet serotonin levels, it can be used in the detection of functioning as well as nonfunctioning tumors. Although its specificity is lower than that of urinary 5-HIAA level (86% and 100%, respectively), its sensitivity is much higher (35% and 68%, respectively) [34] and reported to be the highest in the foregut and functioning tumors. Levels of CgA are correlated with tumor burden [37], and a direct comparison between serum CgA and urinary 5-HIAA levels showed a higher accuracy for CgA in the detection of relapse in carcinoid patients [38]. A significantly worse survival is described in patients with very high levels of CgA (>5,000 μg/l). Data concerning the value of CgA in the follow-up of carcinoid patients to monitor treatment effects are scarce and limited to small series [39].

Nuclear Scintigraphy

[111]In-Pentetreotide Scintigraphy

Somatostatin receptors (SSRs), especially subtype 2 and subtype 5, are located on the cell membranes of carcinoid tumors. Octreotide analogues have a high affinity for the SSR-2 and SSR-5 receptor subtypes and a much lower binding to the SSR-1, SSR-3, and SSR-4 subtypes [40]. ^{111}In-pentetreotide (a radioactive-labeled octreotide analogue) shares the receptor-binding profile of octreotide, which makes it a good radiopharmaceutical for the imaging of carcinoid tumors. The sensitivity of this scintigraphy technique has been reported to range from 80%–90% [41]. Aside from information on the localization of the tumor, a positive finding with ^{111}In-pentetreotide scintigraphy is also predictive of response to octreotide therapy [42].

^{131}I-MIBG (MIBG Scan)

^{131}I-MIBG is an analogue of a biogenic amine precursor and is taken up by chromaffin cells and stored in the

neurosecretory granules. Using ^{131}I-MIBG for the detection and imaging of neuroendocrine tumors was reported in the 1980s followed by papers about the therapeutic applications of ^{131}I-MIBG [43, 44]. The sensitivity of the MIBG scan is reported to be a little lower than that of the ^{111}In-pentetreotide scintigraphy scan (70% versus 85%). However, a direct comparison between these two modalities showed comparable results, with sensitivities of about 84% [41]. A combination of these scans increased the sensitivity to 95% [41].

Bone Scintigraphy

Although ^{111}In-pentetreotide scintigraphy and ^{131}I-MIBG scintigraphy are positive in 70%–80% of carcinoid tumors, in detecting bone metastases, these scans are only positive in 50% and 20% of tumors, respectively [32]. Bone scintigraphy has a high sensitivity of 90%–100% for the detection of these metastases and can be used in patients with the suspicion of bone metastases [32, 33].

Positron Emission Tomography

Positron emission tomography (PET) scanning using ^{18}F-labeled fluorodeoxyglucose ([18]FDG) is widely used as a powerful imaging technique in clinical oncology. Unfortunately, increased FDG uptake in carcinoid tumors is limited due to their low proliferative activity and high differentiation rate. Therefore, several tracers directed toward the specific characteristics of carcinoid tumors, for example, 6-[^{18}F]fluorodopamine (^{18}F-dopa) and ^{11}C-labeled 5-HTP, were developed for PET imaging in these tumors [45, 46]. Although the availability of PET scanning for the clinical diagnosis of carcinoid tumors is still limited, promising results have been described in diagnosing small lesions and lymph node metastases with a sensitivity of up to 65% for ^{18}F-dopa PET [47].

Aside from its role in the staging of carcinoid tumors, uptake of ^{11}C-labeled 5-HTP as a tracer in PET scanning is also of value in follow-up and therapy monitoring [48].

Radiography

Computerized tomography (CT) scanning can be used for visualizing liver metastases, extrahepatic tumor localization in the abdomen (lymph nodes, mesenterial tumor deposition), and tumor localization in the mediastinum and lungs. In addition to follow-up, the findings on CT scan can also be applied in decision making of local treatment options, including resection of metastases in the liver and mesenterium or radiofrequency ablation of liver metastases.

Primary tumors in the small bowel can be demonstrated with barium follow-through, although small primaries are easily missed by this technique.

Video Capsule Endoscopy

Video capsule endoscopy is a new, promising technique for the visualization of the mucosa of the small bowel [49]. The first reports of its use in patients with small-bowel bleeding are promising, and the results are better than those with push endoscopy. In the diagnosis of Crohn's disease, this technique seems to be superior to barium follow-through and CT scan. Experience using the video capsule in carcinoid patients is limited, but the detection of primary carcinoid tumors in the small bowel and early resection is a potential indication for this technique.

Cardiac Evaluation

Detection of CHD at an early stage is important in order to adjust therapy and, hence, improve prognosis. Echocardiography in the follow-up and monitoring of carcinoid patients is the cornerstone for the detection of valvular lesions. However, performing an echocardiography is laborious, expensive, and not always readily available as referral to a cardiologist is necessary. A new development in this field is the detection of cardiac damage using natriuretic peptide (e.g., brain natriuretic peptide [BNP]) levels in the blood. Regular screening of BNP levels might direct the use of cardiac ultrasound and guide treatment strategies [50].

TREATMENT

Supportive Care

As quality of life is severely impaired in patients suffering from the carcinoid syndrome with flushes and diarrhea, supportive care in these patients is essential. Flushes can be reduced by avoiding stress and foods known to provoke symptoms (e.g., alcoholic beverages, spicy meals). Diarrhea can be treated with simple antidiarrheal medications, such as loperamide (Imodium®; McNeil Consumer and Specialty Pharmaceuticals; Fort Washington, PA) and codeine. Severe diarrhea can lead to vitamin deficiencies, and due to the extensive production of serotonin, a depletion in nicotinic acid can occur, which can cause pellagra. Supplementation of vitamins and nicotinic acid is recommended.

Octreotide Analogues

Somatostatin interferes with the release of hormones and neurotransmitters through activation of membrane receptors. Its short half-life (2–4 minutes) limits its clinical application. Octreotide, a somatostatin analogue, has a half-life of 90–120 minutes and can be administered subcutaneously every 6–8 hours. Octreotide can induce symptomatic improvement in up to 80% of patients, although a good clinical response is not always reflected in a reduction of 5-HIAA excretion in urine, as biochemical response is present in 70% of cases

[51]. A positive ^{111}In-pentetreotide scintigraphy scan may be predictive for clinical response to treatment with somatostatin analogues [42]. A major disadvantage of this treatment is the need for subcutaneous injections twice (or sometimes thrice) daily. This drawback may be overcome by slow-release preparations (one intramuscular injection every 2–4 weeks) [52]. In addition to improving symptoms, somatostatin analogues have also been reported to inhibit tumor growth. However, reduction in tumor volume is only occasionally observed.

Interferon-α

Interferon (IFN) was introduced in 1982 as a treatment modality for carcinoid tumors. Although IFN is now widely used in the treatment of carcinoid tumors, its exact mechanism of action is not yet understood. Possible mechanisms are the inhibition of cell proliferation, immune cell–mediated cytotoxicity, inhibition of angiogenesis, and reduction in tumor growth by blocking the cell cycle [53]. Biochemical and subjective responses are reported in 40% and 70% of patients, respectively. A reduction in tumor size is reported in a small minority of patients (about 10%–20%), and the administration of higher dosages of IFN does not increase this response rate. Development of antibodies during treatment with IFN is described in about 5%–20% of patients and seems to be higher with the use of IFN-α2a (Roferon-A®; Roche Laboratories, Inc.; Nutley, NJ) than with IFN-α2b (Intron-A®; Schering-Plough Corporation; Kenilworth, NJ) [54, 55]. The role of these antibodies is controversial. Studies in patients with hepatitis B or hepatitis C did not reveal a relationship between antibody development and therapeutic response [56]. However, in a study of 327 carcinoid patients, high titers of antibodies were associated with a failure of response to treatment, but this phenomenon occurred late in the disease, after a median of 25 months [54].

A synergism in antiproliferative effects of the combination of octreotide and IFN was reported earlier [57]. However, in a recently published prospective study by Faiss et al., there were no differences in response rates among the combination of octreotide and IFN and either therapy alone [39].

MIBG

The use of a tracer dose of ^{131}I-MIBG for the detection and imaging of neuroendocrine tumors was reported in the 1980s followed by papers about therapeutic applications of a higher dose of ^{131}I-MIBG [43, 44]. MIBG is a biogenic amine precursor that resembles noradrenalin. Due to its high affinity for the noradrenalin transporter protein, it is taken up by chromaffin cells and stored in neurosecretory granules. Although MIBG uptake is avid in about 70% of carcinoid tumors, tumor uptake is not always sufficient for therapy. Various applications of MIBG can be used in the treatment of carcinoid patients. Apart from its help in tumor imaging, successful treatment of carcinoid tumors with ^{131}I-MIBG was described in a small series of patients in 1987 [43]. ^{131}I-MIBG was applied at a much higher dose (200 mCi or 7.4 GBq) to provide a selective local effect by internal radiation in the tumor cells in patients with positive ^{131}I-MIBG scans. Significant symptomatic responses were reported in 60% of the patients, with a duration response of 8 months in a prospective study by Taal et al. [58]. The main disadvantage of this treatment is the need for isolation, which is legally required. The administration of unlabelled MIBG was reported in 1996; in carcinoid patients, it resulted in symptomatic responses in 60% of the patients, but with a short median duration of 4–5 months [58]. The cytotoxic effect of unlabelled MIBG is related to inhibition of mitochondrial respiration and is dependent on anaerobic glycolysis, resulting in enhanced glucose consumption, increased lactic acid production, inhibition of oxygen consumption, and reduced ATP levels [59].

Finally, radioactive MIBG after predosing with the unlabelled MIBG resulted in better biodistribution, with more intense MIBG uptake in the tumor. In addition, more patients were eligible for the radioactive treatment after predosing [60].

Radioactive-Labeled Somatostatin Analogues

The somatostatin analogue octreotide has been used since the 1990s for the imaging and treatment of carcinoid tumors. Recently, several radioactive-labeled somatostatin analogues have been developed for use in neuroendocrine tumors with positive ^{111}In-pentetreotide scintigraphy scans. ^{111}In-pentetreotide has a limited radiation range and is suitable for treatment of small tumors or micrometastases. However, clear tumor reduction is only reported in a minority of patients, while symptomatic improvement is observed more frequently [61]. Side effects are mild and restricted to minor hematological toxicities and renal function impairment [62]. Higher tumor radiation can be achieved by application of ^{90}Y and ^{177}Lu, which are beta particles with a wider range of radiation and possibly a higher tumor uptake in neuroendocrine tumor lesions. The first reports of these modalities showed a tumor reduction in about 15%–30% of patients, with clinical benefit in up to 60% [63, 64]. Observed toxicities were nausea and vomiting, hematological toxicities, and some renal function impairment. However, there are some papers reporting the development of end-stage renal failure or myelodysplastic syndrome/leukemia after the administration of radioactive labeled somatostatin analogues [65].

Systemic Chemotherapy

The indication for chemotherapy in neuroendocrine tumors is limited, and it is reserved for high-grade malignancies, which represent only a small minority of this tumor group. Single-agent chemotherapy is not very useful in the treatment of carcinoid tumors, with very low response rates of about 5%–10%. Although schedules with combination chemotherapy have slightly better response rates (15%–30%), these results are still disappointing [66, 67]. A direct comparison between IFN and chemotherapy did not result in a better response rate with chemotherapy [68]. Therefore, chemotherapy is not considered to be a first-line treatment for carcinoid tumors.

Hepatic Artery Chemoembolization

Local treatment of hepatic metastases of carcinoid tumors is attractive because of their slow and localized growth pattern. Liver metastases are usually diffuse at the time of diagnosis, and surgical resection is rarely feasible. Hepatic artery embolization is a local treatment modality of the liver, which may not only ameliorate symptoms but also reduce tumor burden. An objective or biochemical response rate of up to 50% and a median duration of effect of 12 months have been reported in cases failing systemic therapy [69, 70]. Reports on chemoembolization show slightly better biochemical and tumor response rates. Side effects are pain in the liver region, renal toxicity, and elevation of liver enzymes with fever (postembolization syndrome).

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a fairly new technique that can be used for nodules up to 4 cm in diameter in the treatment of unresectable primary and secondary hepatic tumors [71]. The complication rate is 5%–10%, and the mortality rate is low, with a reduction in complications with increasing experience with this technique [72]. The use of RFA in metastases of neuroendocrine tumors has been reported in small series. Local tumor control has been reported in almost all patients, and a symptomatic and biochemical response has been reported in about 60%–80% of patients. However, local recurrence and the development of new metastases are frequently reported [73].

Conclusions

The prognosis for patients with metastatic carcinoid tumors has improved during the last decade. Due to longer survival times, complications, such as CHD, and new metastatic patterns, like skin and bone metastases, may become more important features of carcinoid disease. Follow-up should be focused on monitoring tumor size and extension of metastases by CT scan and nuclear scanning. Special attention should be given to unexpected metastatic patterns, like bone metastases. As survival is poor in patients with CHD, treatment should be focused on reducing elevated levels of hormonal excretion even if there are no symptoms of the carcinoid syndrome. During follow-up, hormonal activity must be monitored on a regular basis. Routine examinations every 6–12 months to detect carcinoid-related heart disease at an early stage are important in order to adjust therapy and, hence, improve prognosis. Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in better quality of life and longer survival times. The increasing number of therapeutic options and diagnostic procedures requires a multidisciplinary approach with a team consisting of an oncologist, a surgeon, a pathologist, a gastroenterologist, a cardiologist, a radiologist, and a nuclear medicine specialist. Decisions should be made in multidisciplinary meetings focused on "tailor-made" therapy based on patients' specific conditions.

Because carcinoid tumors are uncommon, effort should be made to treat these patients in specialized centers and for these centers to join together in multicenter studies.

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