

Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment

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Carcinoid tumors are rare neoplasms which, by tradition, have been divided into foregut, midgut, and hindgut tumors. Although they share many features, they seem to have different molecular backgrounds. Foregut tumors very often show involvement of the *MEN1* gene with deletions and mutations, whereas midgut carcinoids display genetic changes on chromosome 18. Hindgut tumors in general show rather low proliferation capacity, and transforming growth factor- α /epidermal growth factor receptor autocrine mechanism may play a role in the tumor development. Sometimes it might be a problem to delineate the location of the primary carcinoid tumor, but analyzing thyroid transcription factor-1 can be of help, because this factor is only expressed in foregut carcinoid and not in midgut or hindgut tumors. Chromogranin A is an important general tumor marker for all types of carcinoid tumors. Somatostatin receptor scintigraphy is a cornerstone in staging and localization of carcinoid tumors, but newer techniques such as positron emission tomography will challenge its position in the future. Although surgical cure is not obtainable, a more aggressive surgery has emerged during the last decade. Debulking and other cytoreductive procedures are quite common today. Somatostatin analogues have been the treatment of choice in symptomatic patients with carcinoid tumors, but more recent studies have indicated a cytostatic effect of somatostatin analogues. Tumor-targeted radioactive treatment based on somatostatin analogues is now under clinical evaluation. Preliminary data indicate interesting clinical potentials. *Curr Opin Oncol* 2002, 14:38–45 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations

EGF	epidermal growth factor
IMT	L-3–123 iodo- α -methyltyrosine
MIBG	¹²³ meta-iodobenzylguanidin
PET	positron-emission tomography
TGF	transforming growth factor

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By tradition, carcinoid tumors have been divided into foregut, midgut, and hindgut tumors. They belong to a group of neuroendocrine tumors that share many features in their biologic behavior, pathology, growth pattern, clinical syndrome, and treatment. However, a new classification has evolved: the term *carcinoid tumors* is reserved for classical midgut carcinoid tumors secreting serotonin. Other types of carcinoid tumors are called neuroendocrine tumors of the lung, thymus, colon, rectum, and so forth. They are subclassified into the categories well differentiated endocrine tumor, well differentiated endocrine carcinoma, poorly differentiated (small cell) endocrine carcinoma, and mixed exocrine-endocrine tumor [1]. This review uses the old classification because the new one has not been fully accepted world-wide. The review discusses molecular genetics, tumor biology, diagnosis, and treatment of carcinoid tumors from foregut, midgut, and hindgut, regions not including endocrine pancreatic tumors, which were addressed in review in this journal in the year 2000 [2]. Several reviews are recommended on this subject [2–5].

Molecular genetics and tumor biology

Recent studies provide evidence for involvement of a number of genes in the molecular pathogenesis of carcinoid tumors. Mutation of the *MEN1* gene involved in the multiple endocrine neoplasia type-1 syndrome has been reported deleted in the inherited forms of carcinoid tumors [6–8]. Most carcinoids associated with the *MEN1* syndrome have been reported to be of foregut origin. The gene responsible for *MEN1* at locus 11q-13 has recently been cloned, and its involvement in the tumorigenesis of sporadic *MEN1*-associated tumor has been characterized [9,10]. In the carcinoids from the lungs, frequent somatic deletions of the *MEN1* region have been reported using loss of heterozygosity and comparative genomic hybridization analyses [7,8]. In a significant proportion of the cases, inactivating *MEN1* mutations have also been detected. A loss of 11q has been reported in a limited number of carcinoids of ileal, duodenal, and gastric origin. Other frequently detected genetic alterations in carcinoid tumors include losses of 3p, 5q, 9p, 10q, and 13q in lung carcinoids [11]. The *p53* gene, frequently mutated in most human tumors, including gastrointestinal tumors, is only rarely mutated in carcinoids, indicating that *p53* is not important in the tumor genesis of carcinoids [12,13]. Using a comparative genomic hybridization technique, losses at chromosomes 18q and 18p have been reported in 38% and 33%, respectively, of

21 gastrointestinal carcinoids, and in none of 11 bronchial carcinoids. Conversely, deletion of 11q occurred in 36% of bronchial tumors but only in one gastrointestinal tumor [14•]. Similar results have been reported from another group that noticed aberrations at 18q-22 (67%) and losses in 33% of 11q-22 and 22% of 16q-21 in 16 of 18 tumors of midgut origin [15•]. The total number of alterations found in metastases was significantly higher than in primary tumors, indicating an accumulation of genetic changes in the tumor progression. Losses of 18q and 11q were present both in primary tumors and in metastases, whereas loss of 16q and gain of 4p were detected only in metastases [15•]. From these and other studies, it seems that lung carcinoids are more prone to have deletions, losses (mutations) on chromosome 11q, whereas gastrointestinal carcinoids, midguts in particular, show losses of 18q. These findings might indicate that neuroendocrine tumors of the two subgroups develop via different molecular pathways.

Petsman *et al.* [16••], looking particularly at different lung carcinoids, reported loss of heterozygosity in 13 of 20 tumors at 11q-13, but also at 11q-14 through 11q-21 and 11q-25. Atypical carcinoids show loss of heterozygosity at four different regions: the first most proximal region at 11q-13 between markers PYGM and D-11-S-9-137, the second at 11q-14.3 to 11q-21 (D-11-S-906), and the third and fourth defined by markers D-11-S-939 (11q-23.2, 23.3) and D-11-S-910 (11q-25). However, the region 11q-13 harboring the *MEN1* gene was more frequently affected in atypical carcinoids (7/11) than in typical carcinoids (2/9). The high rate of allelic losses within the chromosomal region 11q-13 in atypical carcinoids emphasizes the importance of these regions for tumor development. The authors also recognized that more aggressive atypical carcinoids defined by high mitotic counts, vascular invasion, or organ metastases are combined with increased allelic losses.

A large majority of carcinoid tumors belong to a group of slowly growing neoplasms. However, it has always been a problem to delineate the growth potential in these tumors and, therefore, to make decisions about therapy. A recent study focused on growth characteristics in 50 rectal carcinoid tumors [17••]. *Ki-67*, transforming growth factor (TGF) α , epidermal growth factor (EGF) receptors, *p-53*, *BCL-2*, and apoptosis were analyzed. The authors noticed that the median *Ki-67* labeling index in all lesions was $0.62 \pm 0.59\%$, and the index was significantly higher ($P < 0.01$) in lesions larger than 5 mm. The apoptotic index in all lesions was $0.15 \pm 0.12\%$. The apoptotic index was significantly higher in lesions with higher *Ki-67* labeling index, and did not seem to be related to *p-53* mutations or *BCL-2* induction. TGF- α was expressed more frequently ($P < 0.05$) in lesions larger than 5 mm, and the EGF-receptor was expressed in all lesions. The authors concluded that the proliferation capacity was

very low in rectal carcinoids in general, and that a TGF- α /EGF-receptor autocrine mechanism might play a role in tumor growth.

Goblet cell carcinoids of the appendix were first described in 1974. Dual endocrine and glandular differentiation has led to confusion in the nomenclature (adenocarcinoid, crypt-cell carcinoma, and mucinous carcinoids) [18]. Goblet cell carcinoids are uncommon neoplasms, and their exact biologic behavior is uncertain. In the past, these tumors were alleged to be associated with the same indolent clinical course as conventional carcinoids. However, more recent studies indicate an aggressive behavior [19 20]. Seven cases of goblet cell carcinoids were identified among 110 cases of conventional carcinoids of the appendix. Histopathology revealed widespread infiltration of the periappendiceal fat in all cases, with extensive perineural invasion. The cells stained strongly positive for mucicarmine, periodic acid-Schiff, alcian blue, cytokeratin, and carcinoembryonic antigen. Most cases were positive for synaptophysin. All tumors demonstrated a high cellular proliferation rate, stained by *Ki-67* and proliferating cell nuclear antigen, and also dysregulation of the cell cycle, with upregulation of cycling *D-1* and *p-21* and downregulation of *p-16*. Survival time from diagnosis to death in three patients was 4.6, 5.4, and 19.2 years, indicating unpredictable malignant behavior in [21•].

Another rare group of carcinoids is the thymic carcinoids. These tumors show malignant behavior, and the overall survival rate in these patients is 28% at 5 years and 10% at 10 years, significantly lower than for midgut carcinoids. In a large series of 80 cases of primary thymic carcinoids, the tumors displayed a variegated histologic appearance and unusual cytologic features. Some cases showed transition from low-grade to high-grade within the same tumor. Mitotic activity ranged from fewer than three to more than 10 mitotic figures per 10 high power fields, and most tumors displayed marked cellular atypia and areas of necrosis. A positive immunochemical reaction was observed using antibodies for *CAM 5.2*, low molecular weight cytokeratins, chromogranins, synaptophysin, and leucine 7. The authors recommend changing the term from *carcinoid* to *neuroendocrine carcinoma of the thymus* because of the aggressive biologic behavior of these tumors. Clinically, these tumors exhibited symptoms of Cushing syndrome in 6% and other endocrine abnormalities in 16%. Twenty-eight percent of patients were asymptomatic, and 12% complained about chest pain. Most patients in this series were males (59/80). The mean age was 58 years at diagnosis [22•].

Little is known about prognostic factors for atypical pulmonary carcinoids. In a series of 106 patients, a multivariate analysis showed negative prognostic factor for higher mitotic rate, tumor size of 3.5 cm or greater, and female gender, whereas presence of rosettes were a posi-

tive predictor. The overall 5-year, 10-year, and 15-year survival rates for atypical carcinoids were 61%, 35%, and 28%, respectively. Five-year survival was significantly better for stage 1 and stage 2 than for stages 3 and 4 [23•]. In another study from the Mayo Clinic in patients with atypical pulmonary carcinoid tumors, those patients with regional lymph node metastases had a higher likelihood of developing recurrent disease if treated with surgery alone, and had significantly worse outcome ($P < 0.001$) compared with those patients with typical carcinoid tumors with thoracic lymph node involvement [24•].

The ovary is one of the rare sites for carcinoid growth. In a large series of 8,305 cases of carcinoids in combined registers in United States, ovarian carcinoids are recorded as 0.52% in distribution by site [20]. On the other hand, the distribution rate of these tumors is reported to comprise 1.7% of 3,126 cases in a Japanese series [25,26]. In an analysis of 329 cases of ovarian carcinoids, tumors were divided into two groups: cystic teratoma/dermoid (group A) and those without such lesions (group B). The former group consisted of 189 cases and the latter of 140. There were statistically significant differences between the two groups in tumor size (44.7 mm vs. 89.8 mm), rate of metastases (5.8% vs. 22.1%), and rate of hepatic involvement (2.1% vs. 15%), incidence of associated carcinoid syndrome (13.8% vs. 22.9%), and 5-year survival rate (93.7% vs. 84.0%). Both groups of patients showed insular-type and trabecular-type tumor growth. The carcinoid syndrome was more often evident in tumors of insular type (38.9% vs. 27.8%) [27•].

Diagnosis of carcinoids

Metastatic neuroendocrine neoplasm can have a homogeneous histologic appearance, and without an obvious primary, it may be difficult to determine the site of origin of the metastases. A recent article reported that expression of thyroid transcription factor-1, a nuclear protein expressed during development of the thyroid, lung, and forebrain, can be of help. Thyroid transcription factor-1 was expressed in 80% of metastatic pulmonary carcinoids and no intestinal carcinoids. Other neuroendocrine tumors did not express this factor, either; therefore, this factor might be of value in the clinical workup of patients with neuroendocrine tumors with unknown primary [28•].

The chromogranins A, B, and C make up a family of proteins produced by neuroendocrine tissue. Their precise function is not known, but they serve as precursors to active peptides. Multiple studies over the last 10 years have shown the value of analyzing chromogranin A in patients with neuroendocrine tumors [29,30]. However, in a recent study from Italy, the diagnostic value of plasma chromogranin A in neuroendocrine tumors was challenged. The authors of the study analyzed 80 pa-

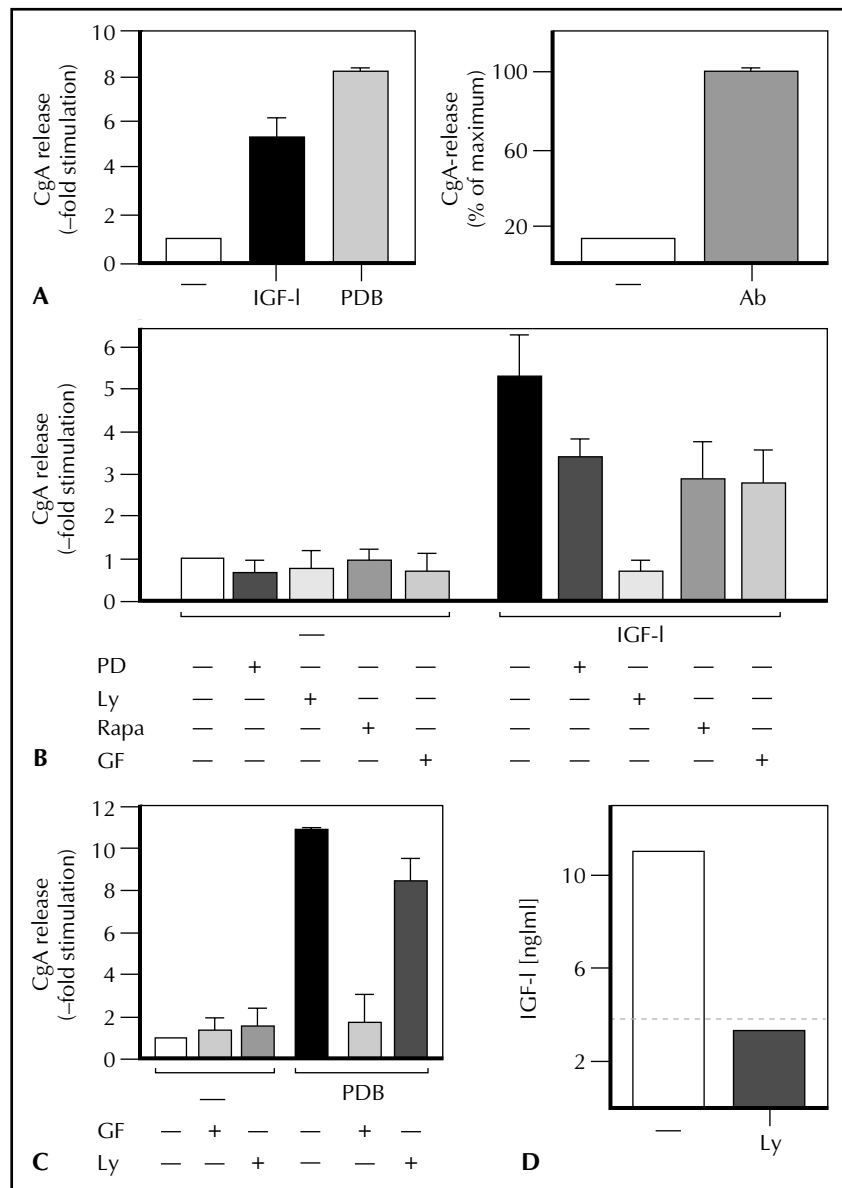
tients with neuroendocrine tumors and found only 45 (56.3%) with abnormally high chromogranin A values. An exception was that nine of 10 gastrinomas showed high elevated chromogranin A. A majority of patients with elevated chromogranin A values had multiple liver metastases [31•]. One explanation for the low frequency of abnormally high chromogranin A levels might be the methods of analysis. The researchers used an enzyme-linked immunosorbent assay from DAKO Denmark A/S (Glostrup, Denmark) that measured not chromogranin A but pancreastatin, a splice product. It is well known that many of these neuroendocrine tumors are not able to splice off pancreastatin [29]. A recent paper from Germany studying a neuroendocrine differentiated cell line, *BONI*, reported that this cell line expressed insulin growth factor receptor and secreted *IGF1*. They could show that exogenously-added *IGF1* induced a marked increase in secretion of chromogranin A, a marker protein for neuroendocrine secretion by a process largely dependent on *PI3* kinase activity. In addition, immunoneutralization of endogenously released *IGF1* markedly reduced basal chromogranin A release by *BON* cells (Fig. 1). Furthermore, *IGF1* stimulated anchorage-dependent and anchorage-independent growth of *BON* cells by pathways involving *PI3*-kinase and *MAP*-kinase activity [32••].

Localization procedures

The localization of neuroendocrine tumors has been significantly improved by the introduction of somatostatin receptor scintigraphy [33,34]. This process is based on the assumption that 80% of neuroendocrine tumors present type-2 somatostatin receptors, which can be targeted by radioactive targeted octreotide. In two recent papers, the somatostatin receptor scintigraphy (^{111}In -pentetreotide) is compared with an old method using ^{123}I -meta-iodobenzylguanidin (MIBG). ^{111}In -pentetreotide scintigraphy was more sensitive in detecting metastatic lesions than MIBG, 67% versus 50% for carcinoid tumors, 91% versus 9% for pancreatic islet cell tumors, and 100% versus 60% for medullary thyroid carcinoma. In only two patients were lesions seen with MIBG scanning that were not apparent with ^{111}In -pentetreotide [35•]. In another study, scintigraphy using a tyrosin analogue, L-3-123 iodo- α -methyltyrosin (IMT) was compared with ^{111}In -indium-octreotide scintigraphy in carcinoid tumor patients. IMT scintigraphy detected only 43% of carcinoid lesions that were positive on ^{111}In -indium-octreotide scintigraphy. The only advantage of using IMT was that the tumor dopamine metabolism was related to IMT uptake [36•]. ^{111}In -indium-octreotide scintigraphy was attempted in a study for the detection of patients with gastric carcinoids. One hundred sixty-two patients with Zollinger-Ellison syndrome were studied prospectively with somatostatin receptor scintigraphy with single photon emission computed tomography. The scan was positive in 19 patients (12%). Sixteen patients

Figure 1.

(A, left panel) IGF-I stimulates chromogranin A secretion in BON cells. Serum-starved BON cells were incubated with 400 nM PDB or 100 ng/ml IGF-I for 30 min, and chromogranin A concentrations in the supernatant of cultured cells were determined using a specific ELISA. (A, right panel) immunoneutralization of IGF-I inhibits basal chromogranin A release by BON cells. Serum-starved BON cells were incubated with 25 µg/ml IGF-I neutralizing antibody for 24 h. The concentration of chromogranin A in the supernatant was subsequently determined using a specific ELISA. (B) IGF-I stimulated chromogranin A secretion is largely dependent on PI3-kinase activity. Serum-starved BON cells were incubated with 20 ng/ml rapamycin (*Rapa*, +), 20 µM PD 098059 (*PD*, +), 3.5 µM GF 109203X (*GF*, +), or 20 µM LY 294002 (*Ly*, +) for 40 min. Control cells received an equivalent amount of solvent (–). Cells were then incubated with 100 ng/ml IGF-I (IGF-I) for 25 min. (C) PDB-stimulated chromogranin A release is dependent on PKC activity but independent of PI3-kinase. Serum-starved BON cells were incubated with 3.5 µM GF 109203X or 20 µM LY 294002 for 40 min. Control cells received an equivalent amount of solvent. Cells were then incubated with 400 nM PDB (*PDB*, +) for 25 min. (D) autocrine IGF-I secretion is mediated by PI3-kinase in BON cells. Serum-starved BON cells were incubated with 20 µM LY 294002 for 24 h. Control cells received an equivalent amount of solvent. The IGF-I concentration in the supernatants of treated and untreated cells was subsequently analyzed using a specific ELISA. Adapted with permission from [32•].



had a gastric carcinoid, and 12 of these patients had a localization by scintigraphy. The sensitivity of somatostatin receptor scintigraphy in localizing gastric carcinoids was 75%, and specificity was 95%. Positive and negative predicted values were 63% and 97%, respectively [37•].

Positron-emission tomography (PET) using short-lived isotopes was reported of value in the diagnosis and localization of neuroendocrine tumors [38]. Eight patients with neuroendocrine tumors, five patients with carcinoids, and three patients with islet cell tumors were investigated by ^{64}Cu -TETA-octreotide as a PET tracer, and the result was compared with ^{111}In -octreotide scan. In six of eight patients, lesions were visible with both methods. In two patients, the ^{64}Cu -TETA-

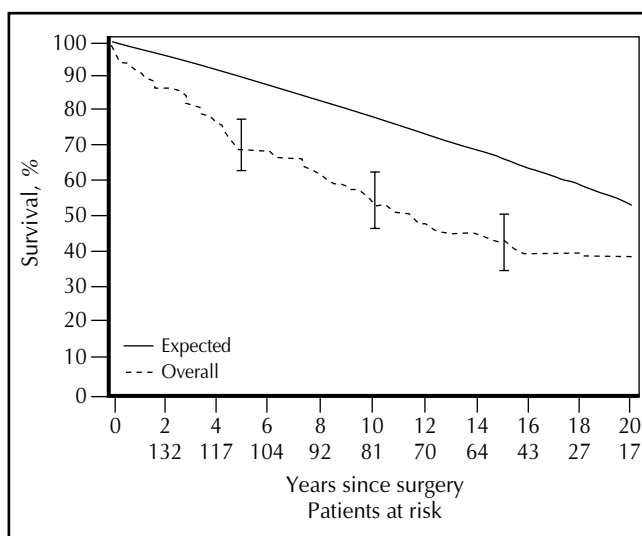
octreotide PET showed more lesions than Octreoscan. The authors concluded that this isotope showed a high rate of lesion detection and was a promising radiopharmaceutical for PET imaging of patients with neuroendocrine tumors [39•].

Treatment of carcinoid tumors

The majority of patients with various carcinoid tumors seek treatment for metastatic disease. Although surgical cure is not obtainable, a more aggressive surgery has emerged during the last decade. Debulking and other cytoreductive procedures are quite common today, as is bypassing [40–42]. In a relatively large series of patients with gastrointestinal carcinoids (N = 154) reported from the Mayo Clinic, 95% underwent surgical or endoscopic excision of the primary tumor, with overall operative

mortality and postoperative morbidity rates of 2.6% and 11%, respectively. At follow-up, 39% of the patients were alive after a median of 18 years. The main causes of death included tumor progression in 32%, unrelated causes in 45%, other malignancies in 19%, and unknown causes in 4%. Observed overall 5-year and 10-year survivals were 69% and 53%, respectively (Fig. 2). Survival was not related to gender or symptoms at examination. However, in a multivariate COX-model analysis, older age (older than 62 years, $P = 0.005$) and hepatic metastases ($p = 0.003$) were associated with a greater risk of death [43•]. In 56 patients with advanced midgut carcinoids, removal of the mesenteric tumor with preservation of the mesenteric vessels was obtainable. The right colon and the mesenteric root were mobilized and released from posterior adhesions. The mesenteric artery was identified below the pancreas, and this artery was free-dissected on the tumor capsule in the mobilized mesentery. The dissection was successful, even with tumors initially judged inoperable, unless tumor growth completely surrounded the mesenteric vessels or extended retroperitoneally. Only one patient was subjected to distal intestinal artery bypass. Symptom relief was substantial and of long duration [44••]. In a German study, 31 patients (17 patients with midgut carcinoids, 10 patients with an endocrine carcinoma of the pancreas, and four patients with carcinoids of the lung) underwent liver resection for a metastatic tumor. Ten patients obtained curative resection, with 5-year survival at 86%. A palliation was obtained in 21 patients, with 5-year survival at 26%. The overall 5-year survival was 47%, with a mean postoperative follow-up of 3.5 years. Postoperative morbidity rate was 13% [45•].

Figure 2. Survival analysis in gastrointestinal carcinoids



One hundred fifty patients with gastrointestinal carcinoids underwent surgical excision of the primary tumor. Observed 5-year and 10-year survival rates were 69% and 53%, respectively.

Cytotoxic treatment has been the gold standard of therapy for patients with malignant endocrine pancreatic tumors but has been less effective in patients with carcinoids [46]. Twenty-four patients were included in a phase II study of high-dose paclitaxel in patients with advanced neuroendocrine tumors. Fourteen patients had carcinoids, nine had islet cell tumors, and one had an anaplastic undefined tumor. The patients received continuous infusion of paclitaxel for 24 hours at a dose of 250 mg/m² every 3 weeks, plus filgrastim at a dose of 5 µg/kg/d subcutaneously. The overall response rate was 8% (95% CI, 0–0.11). The estimated median survival was 1.5 years. Hematologic toxicity was significant, with 12 patients developing grade 4 hematologic toxicity. It is quite obvious from this study that paclitaxel given as high-dose treatment supported by filgrastim is not of benefit as treatment for patients with neuroendocrine tumors [47•].

Somatostatin analogues have been the treatment of choice in symptomatic patients with carcinoid tumors, reporting objective and biochemical response rates in the range of 50 to 70% [46,48–51]. Data indicate that octreotide and lanreotide might have a direct antitumoral effect, with stabilization of tumor growth and reduction of tumor size. In a study from France, 35 consecutive patients with documented tumor progression were treated with somatostatin analogues. The treatments were subcutaneous octreotide 100 µg three times per day (17 patients), intramuscular lanreotide long-acting release every 14 days (11 patients) and both somatostatin analogues successively during the follow-up (seven patients). Primary tumor location was the small intestine in 12 patients, the pancreas in 13, the lung in five, and other sites in five. Eighteen patients were examined for the carcinoid syndrome with flushing, diarrhea, or both. Median duration of treatment was 7 months. Treatment was discontinued in three patients because of side effects. One patient achieved a partial response, and the disease was stabilized in 20 patients (57%) for a median duration of 11 months [52•]. In a study from Italy, 15 patients with metastatic neuroendocrine tumors, seven with midgut carcinoids, and eight with endocrine pancreatic tumors resistant to lanreotide received treatment with slow release octreotide 20 mg every 4 weeks for a median of 8 months. An objective partial response was documented in one patient (7%), stable disease in six (40%), and progressive disease in eight (53%). The progressive disease was noticed in patients with nonfunctioning endocrine pancreatic tumors [53•]. These two studies further indicate that somatostatin analogues act cytostatic with stabilization of tumor growth in approximately 50% of patients for extended periods.

Tumor-targeted radioactive treatment has been performed over the years, initially using ¹³¹I-MIBG [54]. This therapy has been recently updated by a group from Netherlands, with the longest experience of MIBG

therapy in carcinoids. The authors showed that predosing with nonradiolabeled MIBG resulted in improved targeting of ^{131}I -MIBG, with a prolonged palliation and biochemical response in the patients. This finding was further supported by preclinical data in *BON*-carcinoid xenografted mice: predosing with cold MIBG increased tumor/nontumor radioactivity rates by 1.5-fold to three-fold [55•]. However, the objective response rates of MIBG therapy have been limited, with symptomatic improvement in 30 to 40% of patients and biochemical responses in 7 to 10% [54,55•]. Targeted radiotherapy is not an option in patients with a negative or weakly positive MIBG scintigraphy. However, using nonradiolabeled MIBG might enhance uptake in patients with low initial uptake.

Tumor-targeted treatment with radioactive somatostatin analogues has been developed during the last few years [56,57,58]. In a recent study, 41 patients with neuroendocrine tumors were subjected to treatment with ^{90}Y -DOTA-TOC, a β -emitting radionuclide based on octreotide. It binds somatostatin receptors 2 and 5. The treatment consisted of four intravenous injections of a total of 6,000 megabecquerels/ m^2 of ^{90}Y -DOTA-TOC administered at intervals of 6 weeks. The overall response rate was 24%. For endocrine pancreatic tumors, the response rate was 36%. Complete remissions were found in 2%, partial remissions in 22%, and minor responses in 12%. The median follow-up was 15 months. The median duration of response was not reached at 26 months. The two-year survival rate was 76% for neuroendocrine tumors and 83% for endocrine pancreatic tumors. Patients suffering from carcinoid syndrome achieved a significant reduction of symptoms. The treatment was well tolerated. Side effects included grade 3 cytopenia in 5% and vomiting shortly after injection in 23%. No grade 3 or 4 renal toxicity was observed [59••].

Somatostatin-based tumor-targeted radioactive treatment seems promising, and several phase II studies in different neuroendocrine tumors are ongoing worldwide. There is still a problem with kidney toxicity, and infusion of amino acid is now used to reduce the renal peptide reabsorption. The precise role of tumor-targeted radioactive somatostatin analogue treatment must be defined in forthcoming clinical trials.

Conclusions

Carcinoid tumors show rather varied primary tumor location and molecular biology, which will have impacts on diagnosis and therapy. Today somatostatin receptor scintigraphy is a routine procedure in patients with neuroendocrine tumors for staging of the disease and therapy selection. Radioactive somatostatin analogue therapy indicates interesting clinical potentials in patients with malignant disease.

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44 Endocrine tumors

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