REVIEW

Carcinoid tumor

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Abstract

Carcinoid tumors are slow growing malignancies which occur most frequently in the gastrointestinal tract (about 74 %). They can also be found in the bronchus, ovary, lung, thymus, kidney or thyroid gland. Carcinoid tumors are usually identified histologically by their affinity to silver salts, or more specifically by immunocytochemistry using antibodies againts their specific cellular products. Survival rates depend on the location of primary tumor, extent of locoregional and metastatic disease, functional status of the tumor and the feasibility of complete surgical extirpation. Clinical manifestations are often vague or absent. Nevertheless, tumours secrete bioactive mediators which may in approximately of 10 % of patients engender various elements of characteristics of carcinoid syndrome. Patients with advanced carcinoid disease should be treated with aggresive medical and surgical therapies. *(Ref. 103.)*

Key words: carcinoid, Octreoscan, somatostatin analogues, interferon alpha, carcinoid syndrome.

Historic perspective

Lubarsch is credited with the original detail description of carcinoid in 1888 (Lubarsch, 1888). The classic symptomatology of the carcinoid syndrome was reported two years later by Ranson. He described a patient with diarrhea and wheezing, secondary to an ileal carcinoid that had metastasized to the liver. The derivation of carcinoid tumors from argentaffin enterochromaffin cells of the gastrointestinal tract (GI) was postulated by Gosset and Mason in 1914 (Gosset et al, 1907). The description of 5-hydroxytryptamine (5-HT) — serotonin in 1948 was followed by a flurry of discoveries regarding the endocrine potential of carcinoid tumors. The carcinoid syndrome was described by Pernow and Waldenstrom in 1957 (Pernow et al, 1957). In 1955 Page reported the secretion of large quantities of serotonin in the urine in patients with carcinoid syndrome (Lauffer et al, 1999).

Incidence

The overall incidence of carcinoid tumors in the USA has been estimated to be 1—2 cases per 100 000 people (Sweeney et al, 1997).

Because many carcinoid tumors are indolent, their true incidence may be higher. A Swedish study in a single geographic location reported an incidence calculated on surgical specimens and autopsies 8.4 cases per 100 000 people (Kulke et al, 1999).An analysis of 2837 cases in United States found out that appendix was the most common site of carcinoid tumors, folowed by rectum, ileum, lungs, bronchi and stomach (Godwin, 1975).

A recent analysis of 5468 cases has identified by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute between 1973 and 1991 found out an increase in the proportion of pulmonary and gastric carcinoids and a decrease in the proportion af appendiceal carcinoids. These changes in relative incidence may be, in part, due to top variations in the detection and reporting of carcinoid tumors (Modlin et al, 1997).

Carcinoid tumors are generally thought to be sporadic, except for a small proportion that occur as a part of multiple endocrine neoplasia syndromes. Data regarding the familial occurrence of carcinoid, as well as its potential association with other neoplasm are limited. In the study performed by Babovic-Vuksanovic and coworkers 3.7 of patients with carcinoid tumor had at least one

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of their first degree relatives with the same malignancy. The rate of carcinoid tumor in first-degree relatives of probands was higher ($p<0.0001$) than expected, based on the Surveillance, Epidemiology, and End Results population data. Cumulative probability in first-degree relatives for the development of carcinoid was calculated to be 1.5 % at age 80. There was an increased risk of the development of a carcinoid tumor first-degree relatives of patients with carcinoid. Neither patients with carcinoid, nor their first-degree relatives had an increased incidence of other malignancies (Babovic-Vuksanovic et al, 1999).

Classification

The classification schema for neuroendocrine tumors is based on the site of their origin (lung, pancreas, small intestine, ...), tumor size, extension to the surrounding tissue, angioinvasion, biologic behaviour, histologic differentiation and on the functional status of the tumor. Carcinoid tumors may be divided according to the embryologic site of origin. The classification proposed by Wiliams and Sandler identifies tumors as arising from the foregut, midgut or hindgut (Williams et al, 1963). Tumors arising from each region have unique biologic characteristics and can cause different symptoms. Foregut tumors arise in lungs, stomach and duodenum and constituate approximately 15 to 25 % of all carcinoids. They generally have low serotonin content and may produce 5-hydroxytryptophan (5-HTP), corticotropin, gastrin and tachykinins. Midgut tumors are the most common variety of carcinoids. They may arrise in appendix (30 to 50 % of all carcinoids), in the small intestine (15 to 35 % of all carcinoids) or in the right colon (Soga et al, 1999). They produce serotonin and tachykinins and are responsible for the carcinoid syndrome when metastases to the liver are present. Hindgut carcinoids occur less frequently and are found in the distal colon and rectum. These lesions classically do not produce serotonin, substances including SMS, peptide YY, glucagon and glicentin have been imunolocalized to this tumors (Kulke et al, 1999; Memon et al, 1997; Sweeney et al, 1997).

Histologic classification

Many investigators have adopted the classification system that takes into account not only the site of origin but also the variations in histologic characteristics of carcinoid tumors. So-called typical tumors are classified as well-differentiated neuroendocrine tumors. These tumors are characterized by small cells containing regular, well rounded nuclei and have 5 generally accepted growth patterns: insular, trabecular, glandular, undifferentiated and mixed. In the past, tumors with increased nuclear atypia, higher mitotic activity or areas of necrosis have been broadly termed atypical or anaplastic carcinoids. These tumors have more recently been classified as either well-differentiated or poorly differentiated neuroendocrine carcinomas (Capella et al, 1995; Soga et al, 1971; Travis et al, 1998).

Carcinoid are tumors thought to arise from neuroendocrine cells. They are characterized histologically by positive reaction to silver stains and to markers of neuroendocrine tissue, including neuron specific enolase, chromogranin A, B, and synaptophysin (Hammond et al, 1998). When viewed through an electronic microscope, carcinoid tumors are typically found to contain numerous membrane bound neurosecretory granules. These granules are composed of a variety of hormones and biogenic amines. One of the best characterized substances is that of serotonin.

Clinical presentation

The presentation of carcinoid tumor varies according to its site of origin. Bronchial carcinoids are usually slow growing tumors that arise in the proximal bronchus. Patients with typical pulmonary carcinoids (i.e. well differentiated pulmonary neuroendocrine tumors) usually present in the fifth decade of life. The majority of tumors are perihilar in location and primarily produce symptoms of bronchial obstruction, reccurent pneumonia, cough, hemoptysis or chest pain (Kulke et al, 1999). Ectopic secretion of corticotropin from pulmonary carcinoid tumours accounts for 1 % of all cases of Cushing's syndrome (Limper et al, 1992; Arlt et al, 1997). Acromegaly due to ectopic secretion of growth hormone-releasing factor has also been reported (Carroll et al, 1987). The carcinoid syndrome occurs in less than 5 % of patients (Soga et al, 1999). Well differentiated pulmonary neuroendocrine tumors are ussually indolent, with metastases reported in less than 15 % of cases (Torre et al, 1989; Travis et al, 1998). Approximately one third of pulmonary carcinoids have atypical histologic features and are classified as well-differentiated pulmonary neuroendocrine carcinomas (Travis et al, 1998). They occur more commonly in peripheral lung fields and have an aggressive clinical course, metastasizing to mediastinal lymph nodes in 30 to 50 % of cases (Kulke et al, 1999). Risk of 5-year distant metastasis was examined among patients with and without family history of cancer. The proportion of patients with distant metastasis was significantly higher among patients with cancer-positive family history especially among their first degree relatives (index of genetic susceptibility). Bronchial carcinoid tumors are unique 1 to 2 % of primary lung neoplasms and have an excellent prognosis after resection (95 % 5-years and 93 % 10-years survival) (Harpol et al, 1992; Perkins et al, 1997). Thymic carcinoid was described for the first time as a separate entity from thymoma as a part of multiple endocrine neoplasia type I (MEN-I). Predominantly in male patients, heavy smokers at middle age. Prognosis is pure because of late detection (Teh et al, 1997).

Gastric carcinoid tumours were previously thought to be extremely rare lesions. In literature from the pre-endoscopic era, they composed only 0.3 % of all gastric tumours and 1.9 % of all gastrointestinal carcinoids. More recent studies have reported that as many as 10 to 30 % of all carcinoids may occur in the stomach. It has been noted that gastric carcinoids exhibit an increased incidence in individuals with atrophic gastritis and pernicious anemia or combined Zollinger-Ellison syndrome and MEN I (ZES-MEN I) (Hyrdel et al, 1994; Bedrna et al, 1997).

Three distinct tumour types have been proposed: I) gastric carcinoids associated with type A chronic atrophic gastritis (CAG-A), II) gastric carcinoids associated with ZES-MEN I and III) sporadic gastric carcinoids (Hyrdel et al, 1995; Lauffer et al, 1999). Gastric carcinoids arising in CAG/A patients (type I tumors) and ZES-MEN I (type II tumors) are ussually associated with hypergastrinemia. Type I is more frequent, and comprises approximately 65 % of all gastric carcinoids. Sporadic gastric carcinoids (type III tumors) are encountered less frequently (21 %) and display a moderately aggressive behaviour with invasive growth and high incidence of metastasis (Soga et al, 1971; Muller et al, 1992; Rindi et al, 1993; Kolby et al, 1998; Brundler et al, 1999). Carcinoids arising in the stomach are generally incidentally identified unless they produce upper abdominal pain, bleeding or obstruction of gastrointestinal outlet. Sporadic gastric carcinoid tumors have been associated with an atypical carcinoid syndrome that is manifested primarily by flushing that is thought to be mediated by histamine (Kolby et al, 1997).

Midgut tumors occuring in the appendix and small bowel are frequently silent and therefore may be locally advanced when discovered. The presentation of appendiceal carcinoid may be indisinguishable from acute appendicitis. Tumors of the small intestine generally grow slowly and produce symptoms of intermittent abdominal pain and weight loss. Malignant carcinoid, in this region, induce fibrosis in the small bowel mesentery, and are associated with mechanical small bowel obstruction. In the majority of individuals, the diagnosis is not made prior to the surgery (Lauffer et al, 1999). The small intestine is the most frequent location for carcinoid tumours. In an autopsy series by Berge and Linell, carcinoids comprised 95 % of all small intestinal primary tumors, and 88 % of them were incidental (Berge et al, 1976). Patients with small bowel carcinoid in general, are usually in the sixth or seventh decade of life. Five to ten % of them with carcinoide syndrome (Kulke et al, 1999). The appendical carcinoids are most often diagnosed in fourth or fifth decade of life. They are more common in women than in men, the fact of which reflects a greater exposure of young women to surgery and incidental appendectomy (Soga et al, 1971; Memmon et al, 1997). Less than 10 % of appendical carcinoids cause symptoms, because approximately 75 % of them are located in the distal third of the appendix, where they are unlikely to cause obstruction. Most of the remainder are localized in its middle third, and less than 10 % at the base (Bubnoff et al, 1997; Petrušovič et al, 1997; Soga et al, 1999).

Carcinoid tumors of the colon comprise 4.4 % of all carcinoid cases and occure more frequent in the coecum (Spread et al, 1994). Similarly to carcinoid tumors of the small intestine, they are thought to be from serotonin-producing epithelial endocrine cells. Patients with colonic carcinoids most commonly present in their seventh decade of life, symptoms of pain, anorexia or weight loss (Memmon et al, 1997; Kulke et al, 1999). Less than 5 % of patients have carcinoid syndrome (Soga et al, 1999). Approximately two thirds of these tumors are localised in the right side of the colon, most of them in the coecum. Most patients do not become symptomatic until reaching an stage of the disease (Soga et al, 1971).

Rectal carcinoids make up 1 to 2 % of all rectal tumors and are most common in the sixth decade of life. In contrast to carcinoid of small bowel and colon, rectal carcinoids usually contain glucagon and glicentin-related peptides, rather than serotonin (Capella et al, 1995). Rectal carcinoids can cause rectal bleeding and are frequently noted on rectal examination or lower endoscopy.

Malignant carcinoid syndrome

The release of serotonin and other vasoactive substances into the systemic circulation is thought to cause carcinoid syndrome. The carcinoid syndrome occurs in less than 10 % of patients with carcinoid tumors. Clinically, this syndrome develops when vasoactive substances produced by the carcinoid tumor escape hepatic degradation and gain access into the systemic circulation. This is most commonly seen with ileal carcinoid tumors that have metastasized to the liver. Less frequent examples include carcinoid tumors with extensive retroperitoneal involvement that drain into the paravertebral venous system, or primary carcinoid tumors located outside the GI tract (ie bronchial or ovary that do not drain into the portal venous system). The classically described primary features of the carcinoid syndrome include: vasomotor, cardiac or gastrointestinal manifestations.

Flushing occures in 80 % of patients. flushing can be precipitated by stress or by consuming blue cheese, chocolate, alcohol, nuts, bananas and wine. Diarrhea is presented approximately in 75 % of pts with the carcinoid syndrome and is typically associated with episodes of cutaneous flushing. Diarrhea is episodic, watery, often explosive with abdominal cramps, borborygmi and urgency. Malabsorption and steatorhoe may occure. Bronchoconstriction and dyspnea associated with flushing episodes have also been reported in 25 to 30 % patients.

Carcinoid heart disease

Carcinoid heart disease can be detected clinically in aproximately 25 % of patients with carcinoid syndrome. When echocardiography is used, abnormalities are found in 60 % of patients. Cardiac lesions are believed to occur as a result of circulating vasoactive substances produced by the tumor. High plasma levels of serotonin and tachykinins such as neuropeptide K and substance P have been found in pts. with carcinoid heart disease. The presence of cardiac involvement has important prognostic implications. In one series, the median survival was 1.6 yr for pts. with carcinoid heart disease versus 4.6 yrs for pts. in whom cardiac involvement was absent (Pellika et al, 1993). Cardiac surgery has been shown to improve symptoms and prolong survival, but is associated with significant mortality and morbidity because at the time of operation the disease is often advanced. Connolly et al (1995) compared the outcome in the patients who underwent surgery with pts treated medically. Two-year survival in the surgical group was 40 %, compared with 8 % in the medical group. The most common cardiac finding is the precordial systolic murmur consistent with tricuspid regurgitation. In some pts there may be a diastolic murmur due to pulmonary

regurgitation or tricuspid stenosis. In the largest reported series (Pellika et al, 1993) tricuspid involvement was observed in 97 % and pulmonic involvement in 88 % of patients. Characteristically, tricuspid leaflets appear thickened, immobile, retracted and in the most serious cases fixed in a partially opened position. Tricuspid regurgitation is present in nearly all cases, and ussually moderate or severe, tricuspid stenosis may also be present. Left sided involvement is rare, and occurs in the presence of carcinoid tumors of the lung or patent foramen ovale. There seems to be no relationship between the severity of cardiac disease and the presence of other symptoms. Biventricular failure with acute pericarditis and constrictive pericarditis were also described (Denney, 1998; Vergani, 1998; Johnston, 1999).

Diagnosis — Imaging modalities

Primary neuroendocrine tumours (NETs) are often small and grow slowly. This often makes their identification and localization difficult, especially in the stages. For the diagnosis and management purposes, identification of the primary tumor and metastases is mandatory. Several technics are available to evaluate the primary location and extent of disease in carcinoid tumors. Conventional radiologic techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and angiography are well established as advanced tools for NET identification. CT scanning is highly accurate and non-invasive. For CT scanning to be useful for the detection of NETs, advanced dynamic scanning techniques with rapid contrast injection are required (Shi et al, 1998). MRI has been shown to be effective for detecting tumors in both liver and pancreas and more sensitive than CT (Reining et al, 1987).

Patients with signs and symptoms suggestive of bronchial carcinoid should undergo bronchoscopy and computed tomography scan of the chest. On bronchoscopy, foregut carcinoids appear as deep pink or red tumors that protrude into the bronchial lumen (Sweeney et al, 1997). Carcinoid tumors of the stomach are usually identified with upper endoscopy or upper gastrointestinal (GI) series during the evaluation of peptic ulcer symptoms or upper GI bleeding. Upper and lower endoscopy, enteroclysis, and computed tomography (CT) scans of abdomen and pelvis are helpful in evaluating the spread of the tumor to the liver and regional lymph nodes (Bubnoff et al, 1997; Kulke et al, 1999). Midgut tumors are associated with tumor extension into the mesentery and distant spread to the liver. They frequently cause retroperitoneal fibrosis and ureteric obstruction. Mesenteric angiography may show caliber changes or occlusion of blood vessels suggesting tumor encasement of the superior mesenteric artery or its branches (Lauffer et al, 1997). If available, endoscopic ultrasound, is a highly sensitive method for detecting carcinoid tumors of the proximal gut (Rosch et al, 1992). In comparison to conventional ultrasound it is clearly superior, particularly in the detection of small lesions localized at the bowel wall (Zimmer et al, 1994).

Imaging modalities of nuclear medicine include positron emission tomography (PET), Octreoscan and I 131 metaiodine benzylguanidin scintigraphy. Positron emission tomography is superior to computed tomography or ultrasound because it detects more lesions, outlines them better, and provides information about biochemical and metabolic changes in the tumor tissue after treatment. It can be used in the follow-up of the patient's disease course as well (Eriksson et al, 1994). Somatostatin receptor scintigraphy using indium 111 pentetreotide has shown encouraging results in tumor localization. A number of studies report higher sensitivity of scintigraphy (80—90 %) compared with conventional methods such as computed tomography (60—70 %) in both delineating and localising tumors (Krenning et al, 1993; Kwekkeboom et al, 1993; Krenning et al, 1994; Hammond et al, 1994; Modlin et al, 1995; Seifert et al, 1997; Frilling et al, 1998). This modality also allows simultaneous visualization of metastases in every region of the body, as well as detection of unsuspected tumor sites, usually not diagnosed with the use of other imaging modalities.

The amount injected is 6mCi of 111 In-labelled Octreotide. Whole-body scintigraphy is performed directly following the injection, further scans are made 1, 2, 4 and 20 hours later. In 111, pentetreotid is accumulated in the spleen and in the liver as well as in receptor positive tumor tissue. Receptor scintigraphy with SMS analogues is a very sensitive method for the demonstration of receptor positive tumors and their metastases, particularly in tumors expressing somatostatin receptor (SSTR) type 2 and 5 for which octreotide has a particulary high affinity (Krenning et al, 1994; Nilsson et al, 1998). The degree of accumulation in scintigram corresponds with receptor density in the tissue. All body regions are covered by whole body scintigraphy. Small tumors and previously unknown metastases are detectable (Krenning et al, 1993; Jais et al, 1997; Lamberts et al, 1993; Lauffer et al, 1999; Kaltsas et al, 2000). The sensitivity of the study can be further enhanced by simultaneous using of single positron emission computed tomography (SPECT) imaging (Lauffer et al, 1999). From radiographic results it is known that there is a close relationship between receptor density and the hormone-suppresing effect of treatment with SMS analogues (Kvols, 1986). Meta-iodobenzylguanidine (MIBG) is a catecholamine analog that uses the amine precursor uptake mechanism and may thus be incorporated into vesicles or neurosecretory granules in the cytoplasm. The sensitivity of carcinoid tumor using imaging MIBG is 40 % to 60 % (Feldman et al, 1986; Taal et al, 2000; Kaltsas et al, 2001).

Biochemical characterization

Serotonin is synthetised from its precursor 5-hydroxytryptophan by the enzyme aromatic acid decarboxylase. Serotonin is subsequently metabolized by monoamine oxidase to 5-hydroxyindolacetic acid (5-HIAA), which is excreted in urine. The rate limiting step in the synthesis of serotonin is the conversion of tryptophan to 5-hydroxytryptophan. This is then rapidly converted to serotonin by the enzyme dopadecarboxylase. The foregut tumors are deficient in dopa decarboxylase activity and therefore secrete low serotonin and higher amounts of 5-HTP

into the vascular compartment. The 5-HTP is then converted to serotonin and 5-HIAA at extra-renal sites and excreted into urine (Kulke et al, 1999). The classic midgut carcinoids produce serotonin, which is stored in secretory granules of platelets, the rest is converted into 5-HIAA by monoamine oxydase and aldehyde dehydrogenase. Generally, hindgut carcinoids do not produce any of these biochemical compounds but may secret SMS, neurotensin, PP and dopamine. In addition, carcinoid tumors have been found to secrete corticotropin, histamine, dopamine, substance P, neurokinin, neurotensin, prostaglandins and kallikrein (Kolby et al, 1998; Hammond et al, 1998). The classic biochemical identification of carcinoid tumors involves quantifying the excretion of 5-HIAA in a 24 h urine sample. Normal values range is between 10 to 35 μmol per 24 h period. Patients with normal 24 h excretion of 5-HIAA may undergo provocative testing with pentagastrin if high clinical suspicion for carcinoid tumor exists. Another option is in analysis of the main histamine metabolite, methylimidazol acetic acid (MeImAA) in urine (Modlin et al, 1997).

The measurement of serotonin metabolite 5-HIAA in 24 h urine collection may be useful in confirming the diagnosis and in subsequent monitoring of patients with metastatic carcinoid tumors. In one study involving primarily patients with metastatic disease, elevated urinary 5-HIAA excretion predicted the presence of carcinoid tumor with a sensitivity of 73 % and specificity of 100 % (Feldman et al, 1986). The measurements of chromogranin has also been reported to be useful in detecting carcinoid tumors (Eriksson et al, 1990).

Markers of neuroendocrine tissue

Neuron specific enolase (NSE) is one of the markers of neurorndocrine tissue. Plasmatic level of NSE can be useful in the follow-up of patients with malignant carcinoid. Owing to its widespread distribution in euroendocrine tissue, chromogranin A (CgA) can be used as an excellent immunohistochemical marker of neoplasm of neuroendocrine origin. This is because it may be also elevated in many cases of less well-differentiated tumors that do not secrete known hormones. Chromogranin A serum or plasma levels reflect the tumor load and it may be an independent marker of prognosis in patients with midgut carcinoids (Hammond et al, 1998; Nobels et al, 1998; Eriksson et al, 2000). As chromogranin A is a very stable molecule, no special precautions are needed to handle or store the serum samples.

Therapy of the carcinoid

Surgery is the primary treatment for carcinoid tumor.

Gastric carcinoid tumors can be divided histologically to 3 groups: up to 75 % of gastric carcinoid tumors are associated with CAG-A. Lesions less than 1 cm in diameter have been successfully treated with endoscopic resection. Patients with larger, multipple or recurrent tumors have generally undergone more extensive surgical resection — antrectomy. 15 to 25 % of gastric carcinoids are sporadic, majority of them are metastatic at the time of presentation, and the disease is often fatal. Because of the aggressive nature of these lesions, most of them are treated with radical gastrectomy.

Over 95 % of appendical carcinoid tumors are less than 2 cm in diameter. Patients with tumor less than 2 cm are ussually treated by simple appendectomy if there is no clear evidence of local spreading. Most tumors carger than 2 cm in diameter are treated with right colectomy. Small bowels resection with resection of the associated mesentery is the treatment of choice for small bowel carcinoids. Carcinoid tumors of the colon are treated with radical colectomy. Rectal tumors of size less than 1 cm are successfully treated by local resection. Tumors more than 2 cm in diameter have traditionally been treated by low anterior resection or abdominoperineal resection (Memon, 1997; Pešková et al., 1997; Lauffer et al, 1998; Kulke et al, 1999). Conservative resection, consisting of wedge or segmental resection, is currently the preferred form of treatment of localised pulmonary carcinoid tumors. This procedure has resulted in low rates of recurrence and excellent long-term survival.

Management of hepatic metastases

Carcinoid tumors are the most common neuroendocrine neoplasms likely to develop liver metastases. Patients with neuroendocrine malignancies metastatic to the liver often succumb to complications related to excessive hormone secretion, in contrast to patients with colorectal carcinoma in whom death often results from liver failure resulting from hepatic replacement by tumor. Althought few patients with metastatic carcinoid tumors can be cured, significant palliation may be afforded by cytoreductive measures. Surgical resection of liver metastases may be of benefit with limited hepatic disease. Hepatic artery occlusion or embolization is an alternative for patients who are not candidates for hepatic resection. Focal ablative techniques such as cryotherapy, ethanol ablation and laparoscopic thermal ablation have also been used in such tumors. Unfortunately, the duration of the response is often very short (less than 7 months) (Persson et al, 1989; Clouse et al, 1994; Cozzi et al, 1995; Sweeney et al, 1997; Sipperstein et al, 1997; Eriksson et al, 1998).

The role of liver transplantation in the treatment of metastatic carcinoid syndrome is still unclear.

Chemotherapy

Cytotoxic therapy has had only limited success in the treatment of metastatic carcinoid tumors. A variety of chemotherapeutic drugs have been investigated in patients with unresectable or metastatic tumors, including streptozotocin (STZ), doxorubicin, 5-fluorouracyl (5-FU), dacarbazin, cyclophosphamid (CFM) and cis platine. The overall response rates of combined chemotherapy in patients with carcinoid tumors is between 10 to 30 % (Moertel et al, 1991; Muller et al, 1992). In the study performed by Bajeta, patients were treated with 5-FU in the dosis of 500 mg/m^2, dacarbazin 200 mg/m^2, epirubicin 30 mg/m^2 for 3 consecutive days and cycles repeated every 3 weeks. No com-

plete remision was achieved. Partial remission was achieved in 17 %. The disease was stable in 33 %. The treatment has failed in half of the patients (Bajetta et al, 1998). The response rates in other studies performed by Moertel, and by Oberg, where patients were treated with STZ and 5-FU, or STZ and CFM, were between 10 to 40 %, and the duration of response was also very short between 3 to 7 weeks. In the study performed by Moertel and colleagues, 45 patients with metastatic neuroendocrine tumors were treated with regimen of etoposide 130 mg/m^2/day + cis platin 45 mg/m^2/day on days 2 and 3. In 27 patients with well differentiated carcinoid or islet cell carcinoma, only in 7 % the partial regression was seen. In 18 patients with anaplastic neuroendocrine carcinomas the overall regression rate of 67 % was seen. All these studies showed that chemotherapy can be useful only in groups of patinetns with anaplastic neuroendocrine carcinomas (Moertel et al, 1991).

The role of somatostatine in treatment of carcinoid

Somatostatine (SMS) is a paracrine hormone that is known to regulate the growth and secretion of a number of endocrine cells. SMS is a tetradecapeptide with potent inhibitory actions that inhibits the synthesis and release of a brode range of hormones including growth hormone, insulin, glucagon and gastrin. It acts by binding to SMS receptors. SMS receptors are expressed in more than 80 % of carcinoid tumors. The optimal dosage of SMS analogues for long-term control of carcinoid tumors was not established. In some studies octreotid was given as the first line of treatment at an initial dose of 50 µg per day. With regard to the 5-HIAA level, the dose was adjusted during the 9 years of follow-up with good results (Corleto et al, 2000). Effect of octreotide depends on somatostatine receptors.

Somatostatine receptors

SMS receptors belong to the superfamily of G-protein coupled receptors. Activation of somatostatin receptor (SSTR) results in inhibition of adenylcyclase, activation of pottasium channels, stimulation of tyrosine phosphatase activity and in the decrease of conductance of voltage sensitive calcium channels. The rationale for the somatostatin analog therapy is based on the observation that carcinoid symptoms are brouhgt about by the secretion of peptides and amines from the tumors. SMS and its analogs not only suppress the release of these mediators, but also inhibit their action against target tissue. For this reason, the decrease in number of symptoms is more profound that can be accounted for by the degree of suppresion or release of mediator peptide (Wynick et al, 1991; Debas et al, 1993; Anthony et al, 1993; Eriksson et al, 1997).

SMS has also an antitrophic action. Many neuroendocrine tumors express somatostatine receptors. When activated they, slow down the growth and proliferation of some of the cells. So far, five different receptor subtypes have been identified. We know that in forgut carcinoid, all 5 types of SSTR are localised. In the midgut carcinoid only SSTR 2, 4, 5, and in hindgut carcinoids SSTR 2, 4, 5 are present. This information is very useful, because we known that the affinity of SMS analogues to SSTR receptor differs (Katakami et al, 1995; Herder et al, 1996; Szilvas et al, 1998; Wymenga, 1999; O'Toole et al, 2000).

Antiproliferative effects of somatostatine

SMS analogues at high dosis have been shown to induce apoptosis. Antiproliferative effects are mediated through inhibition of autocrine and endocrine growth factors. The antiprolliferative effects of SMS have been shown to be mediated by receptors subtypes 1, 2 and 5 via activation of tyrosine phosphatase or changes in intracellular calcium mobilization.

SMS and its analogues activate primarily the receptor subtypes 2 and 5. Apoptosis of tumor cell is mediated by SSTR-3 which is present in foregut carcinoids but not in midgut or hindgut carcinoids. On the other hand, the affinity of SMS analogues to SSTR 3 is 10-fold lower for SSTR-2. The therapy with SMS analogues improves the symptoms in 70 to 88 % of patients and decreases 5-HIAA excretion in urine samples in 50 to 72 % of patients, however without significant tumor mass reduction.

The largest clinical experience is that reported by Kvols from the Mayo Clinic. In 66 patients with carcinoid syndrome refractory to other forms of therapy treated with octreotide — sandostatin, complete or non complete control of diarrhea was obtained in 77 %, flushing in 87 %, and a 50 % or larger reduction in urinary 5-HIAA was achieved in 77 %. The mean survival of patients was 3 years. Several other smaller studies reported similar findings. The subcutaneous doses of octreotide have varied from 50 to 250 µg three times a day. The major disadvantage of octreotide treatment is that it must be administered subcutaneously two or three times per day.

Native somatostatine is on the basis of short plasma half life of only 2—3 minutes, and therefore must be applicated in continual i.v. infusion. Lanreotide is a slow release analog of SMS due to microspheres containing polylactide polyglicolide copolymer. Lanreotide allows patients to receive one injection in the dosis of 30 mg i.m. every two weeks. Another long acting SMS analogue is Somatostatine LAR in the dosis of 10 to 30 mg i.m. every 28 days. SMS analogues have also been found very effective in the treatment of carcinoid crisis characterised by profound hypotension and tachycardia. In this situation, the best mode of their application is by rapid i.v. infusion (Ruszniewski et al, 1996; Kiňová et al, 1996; O'Toole et al, 2000).

Adverse effects of somatostatine analogues

Pain in the injection site due to acid pH of the solution. Abdominal cramping, bloating, flatulence, nausea and vomiting may be seen initially but this subsides with time. Hyperglycemia and abnormal glucose tolerance has been observed more frequently. Transient elevation in serum transaminase has also been reported. Long-term therapy brings about pancreatic exocrine insufficiency and steatorrhoe. This is well controlled with oral pancreatic enzyme replacement. Pancreatic exocrine insufficiency oc-

curs because of the inhibition of the release and action of cholecystokinin (CCK) as well as the direct inhibitory impact of SMS on acinar cell function. 20 to 25 % of patients treated by long-term therapy will develop gallstones (Wynick et, 1991; Eriksson et al, 1996; Memmon et al, 1997; Sweeney et al, 1997).

Interferon alpha therapy in advanced carcinoid tumors

Over the past decade, biotherapy with interferon alpha (IFN) has been used in patients with carcinoid tumors. The ability of leukocyte interferone to stimulate T-lymphocyte function and to control the secretion of tumor products has led to its initial use in patients with carcinoide syndrome.

The mechanism of interferon inhibition of tumor growth has not been elucidated completely. Its impact on the cell cycle with the prolongation of the S-phase, impairment of hormone synthesis, induction of the nuclear enzyme 2,5 A synthetase, reduction of the amount of viable tumor cells within metastatic lesions followed by an increase in fibrotic tissue and antiangiogenic effects have been postulated as possible mechanisms of antitumor action of alpha interferon. The rResearch has shown reductions in tumor markers in about 45 to 50 % of patients, but the tumor mass was objectively reduced only in 10 to 15 % of patients. Stabilization of disease has been seen in 30 to 40 % and progression of disease in 15 to 20 % of cases. Although clinical symptoms improved in 60 to 80 % of patients a substantial incidence of side effect has also been reported. Dosis of IFN is 3—6 MU s.c. three times/week (Muller et al, 1992; Bubnoff et al, 1997; Oberg, 1997; Frank et al, 1999; Kulke et al, 1999).

Recent studies indicate that a combination of SMS analogs and interferone alpha might give additive or synergic effects at least in terms of biochemical and symptomatic effects. No significant tumor reduction was noted. In the study performed by Frank and coworkers published in American Journal of gastroenterology (1999) the median duration of response to combined therapy tended to be longer in patients with carcinoid syndrome compared with patients with other tumor entities.

In summary, in patients with metastasized carcinoid failing octreotide monotherapy, the addition of IFN alpha seems to provide further antiproliferative efficacy in about twoo-thirds suggesting that the combination treatment is superior to octreotide monotherapy (Eriksson et al, 1999). Compared to cytoreductive strategies, as chemoembolization and debulking surgery or chemotherapy using streptozotocin/doxorubicin combination, this regimen of octreotide plus alpha interferon has the advantage of beeing noninvasive and having mininal toxicity. Several prospective randomized comparison trials are currently in progress (Boehme et al, 1995; Frank et al, 1999; Sweeney et al, 1999; Kiňová et al, 2001).

Radionuclid therapy

MIBG can replace catecholamines from the natural tissue and may induce better biodistribution of radioactive MIBG in tumor. If sufficient MIBG accumulates in tumor sites, compared with normal tissues, another therapeutic option is local irradiation of tumor using a high therapeutic dose — 200 mCi of I 131 MIBG (7.4 GBq). Symptomatic improvement was found in 60 % of patients, although the biochemical response occured only in 7 %. The main advantage of this treatment is the long-term palliative effect with the median of 8 months. Iodine-131-MIBG therapy can provide prolonged symptomatic relief and improved quality of life in patients with metastatic carcinoid disease defying other therapies (Prvulovich et al, 1998; Taal et al, 2000).

From experimental studies it is well known that the SSTR receptor complex is internalised by SSTR positive neuroendocrine tumors. Preliminary data suggest that both somatostatine analogues coupled with beta emmiting isotopes and chemotherapeutic drugs internalised offer new opportunities to specific SSTR-mediated therapy in patients with inoperable tumors (Virgolini, 1997; Virgolini et al, 1998).

The quality of life in patients with carcinoid syndrome is also very important. The effect of short-term treatment with the highly selective serotonin receptor antagonist ondasetron was studied. Ondasetron reduces symptoms of watery diarrhoe due to alteration in gut motor function including postprandial colonic response. It induced no changes in biochemical parameters of serotonin metabolism (Wymenga et al, 1998).

Prognosis and survival

In general, the survival rates are directly related to both site of the primary tumor and the evidence of distant metastases. Despite the fact, that age, stage, region of origin, and urinary level of 5-hydroxyindolacetic acid predicted survival by univariate analysis, only the latter three were indepedent predictors of survival by multivariate analysis. The overall of 5-year survival is excellent for carcinoids of the bronchus (90—95 %), appendix (86 %) and rectum (72 %), whereas small intestinal (55 %), gastric (49 %), colonic carcinoids (42 %) and advanced disease with hepatic metastases (30 %) bring about a far worse prognosis (Lauffer et al, 1999; Onaitis et al, 2000).

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