Acta Oncologica Vol. 32, No. 2, pp. 197–201, 1993

METASTATIC CARCINOID TUMORS AND THE MALIGNANT CARCINOID SYNDROME

LARRY K. KVOLS and JEAN CLAUDE REUBI

Patients with metastatic carcinoid tumors and the malignant carcinoid syndrome have benefited immensely from diagnostic and therapeutic advances during the past decade. Magnetic resonance imaging and whole body scintigraphy with radiolabelled analogues of somatostatin have improved our ability to diagnose, detect, stage and follow response to therapy. Surgical, medical, and radiation therapy may all contribute to the management of these patients. This disease is variable in its presenting symptoms and the biologic behavior of the tumor. The spectrum of clinical manifestations varies depending upon the type and quantity of polypeptide hormones or biogenic amines being produced. Although the tumors are usually indolent in their growth, the more dedifferentiated or anaplastic tumors can be quite aggressive. Thanks to new treatments that are very effective in the subgroup of anaplastic neuroendocrine carcinomas it is vital to recognize this subset. As research scientists and clinicians we must be aware of the natural history of the disease in order to optimize each patient's treatment. This highly selective review focuses on studies performed in collaboration with Dr. Charles Moertel along with other colleagues at the Mayo Clinic, have done in the past few years.

In the vast majority of cases the carcinoid syndrome is associated with carcinoid tumors of the small intestine which have metastasized to the liver. Less frequently it is seen with primary tumors arising from other organs, such as the lung, pancreas, stomach, or ovary. Although I also see metastatic colorectal and thymic carcinoids in my practice, they are rarely associated with the carcinoid syndrome. Episodic flushing and diarrhea are the most common initial symptoms. Some patients may only experience flushing, whereas others may only have the diarrheal component of the syndrome. In approximately 20% of patients, symptoms of congestive heart failure from carcinoid heart disease will be the presenting manifestation. Occasionally, wheezing secondary to bronchospasm, will be the dominant clinical problem.

Metastatic disease may require no treatment for months or even years in the patient whose symptoms are not seriously interfering with their lifestyle and if the tumor is not exhibiting a biologically aggressive growth pattern. In the patient with troublesome or serious symptoms or progressive tumor there are numerous therapeutic options available. These treatments cover the spectrum from simple oral medications, subcutaneous injections with the somatostatin analogue, octreotide, or injections with interferon, to hepatic vascular occlusive procedures followed by aggressive cytotoxic chemotherapy regimes. Therefore, it is important to consider the severity of the symptoms in association with the effect of the disease on vital organ function and tailor the therapy appropriately for the clinical situation.

Diagnostic studies

Once a biopsy of tumor has established that the tissue is consistent with carcinoid, the analysis of 24-h urine collec-

Received 17 October 1992.
Accepted 21 November 1992.
From the Department of Oncology, Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA (L. K. Krols) and Div. of Cell Biology and Experimental Cancer Research, Inst. of Pathology, University of Berne, Berne, Switzerland (J. C. Reubi).
Correspondence to: Dr Larry K. Kvols, Department of Oncology, Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
Presented at the 3rd International Workshop on Neuroendocrine Tumors held in Lofoten, Norway, June 24–28, 1992.

tions for 5-hydroxyindolacetic acid (5-HIAA) remains the most important test to assess functionality of the tumor. In our laboratory the value in normal individuals ranges from 0 to 6 mg per 24 h. Patients with the carcinoid syndrome may have levels only 2–4 times normal but the value may be as high 800–1 000 mg/24 h. This metabolite of serotinin is not always elevated in patients with the carcinoid syndrome, but in the vast majority of patients whose tumors produce serotonin, the level correlates with the severity of the syndrome and with changes in the tumor mass. Many patients will co-secrete the tachykinin, substance P, and this may be one of the key mediators of carcinoid flushing and wheezing.

The 24-h urine 5-HIAA value is highly reproducible in the individual patient. After analyzing two values determined within 7–10 days of each other, and no intervening change in therapy, we concluded that the statistical likelihood of a $\geqslant 50\%$ variability is less than one per hundred. I advise my patients to avoid serotonin-rich foods, such as tomatoes, bananas, kiwi, pineapple, walnuts and pecans just before and during a urine collection, even though large quantities of these items must be ingested to create a false value. Since they do not precipitate or worsen the symptom complex, it should be mentioned to the patient that there is no reason to avoid these foods at other times.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the liver is an excellent tool for diagnosis and follow-up of patients with metastatic carcinoid. The boundaries of heptatic metastases are sometimes better seen with MRI of the liver than with dynamic contrast-enhanced CT scans. Although delayed CT images, 3–4 h after contrast, may show well-circumscribed images, most patients prefer MRI since they do not need to take oral contrast material which almost invariably aggravates their diarrhea. Liver metastases are usually homogeneous lesions of medium signal intensity on T2-weighted images. Necrosis and hemorrhage may also be identified within the metastases. In the initial evaluation of patients with the malignant carcinoid syndrome I also request sagittal views of the thoracic and lumbar spine to look for occult and often asymptomatic osseous metastases. If suspicious lesions are seen in the spine, a radionuclide bone scan will be obtained to image the remainder of the skeleton. The disadvantage of MRI is that it is not available at all medical centers, it is still quite costly, and some patients have claustrophobia. The latter problem may be overcome with modest doses of a mild tranquilizer.

Radiolabelled somatostatin

We have imaged somatostatin receptors (SS-R) in vivo after the injection of Tyr^3-octreotide labeled with 123 iodine. Primary tumors of their metastases were visualized in 13 of the 14 patients with metastatic carcinoids. We also studied 14 patients with metastatic islet cell carcinoma. In three of the 13 with positive scans previously unsuspected lesions were identified. Primary tumors or their metastases were visualized in 10 of the 14 patients with ICC. In one of the 10 patients previously unsuspected lesions were identified. Among all 28 patients there were 16 who also had tumor biopsies analyzed for SS-R using tissue autoradiography. In 13 of these 16, the tumor biopsies tested positive for SS-R and all 13 of these patients had positive scans. In the 3 whose tumor biopsies tested negative for SS-R, 2 had negative scans and in one the number of lesions seen was far less than on the CT scan. In 10 of the 28 patients therapeutic response to chronic administration of octreotide could also be correlated. Nine of the 10 had biopsies positive for SS-R, positive scans, and responded clinically and hormonally to octreotide. The other patient had a negative scan, a biopsy negative for SS-R and no response to therapy with octreotide.

Somatostain receptors

In an effort to see if the presence of somatostatin receptors might predict responsiveness of carcinoid and other neuroendocrine malignancies to octreotide we obtained tumor biopsies on 31 patients with functioning metastatic tumors (carcinoids n = 20, islet cell carcinoma (ICC) n = 8, and medullary thyroid carcinoma (MTC) n = 3) and correlated the hormonal response with receptor assay results. Hormonal responses were defined as follows: a major response was a $\geqslant 50\%$ reduction in the pathologically elevated hormone or its metabolite, a minor response was a 25–49% reduction and no response was $\leqslant 25\%$ reduction or an increase. Receptor assay results were quantitated and reported as very strongly positive (+++), strongly positive (++), positive (+), or negative. Receptors were present in 16/20 carcinoid patients, 8/8 ICC and none of the patients with MTC. Correlation of receptor status with hormonal responses are shown in the Table.

Table

Correlation of tumor somatostatin receptor status with hormonal changes in patients given the somatostatin analogue, octreotide

	Hormonal response		
Receptor status	Major	Minor	No response
+++ positive	9	0	0
++ positive	7	1	0
+ positive	3	3	1
negative	0	1	6

The vast majority of carcinoid patients have somatostatin receptors expressed on the surface of their tumor cells (1). Usually they are homogeneously distributed so the whole body can be imaged shortly after intravenous injection of radiolabelled somatostatin. This is useful for staging since asymptomatic metastases may be detected in lymph nodes, lungs, and skeletal structures. Since the presence of receptors correlates so strongly with hormonal responsiveness, whole body scintigraphy with radiolabelled somatostatin is also useful for predicting which patients are likely to benefit from treatment with the somatostatin analogue, octreotide.

Echocardiography

From January 1980 through December 1989, there were 132 patients referred to the Echo laboratory with the diagnosis of the carcinoid syndrome. Of these patients, 74 (56%) had an echo diagnosis of carcinoid heart disease. The mean level of the 24-h 5-HIAA was 270 mg (normal 0–6). In contrast, the 51 patients without carcinoid heart disease had a mean 24-h 5-HIAA level of 131 mg.

Seventy of the 74 patients with carcinoid heart disease had tricuspid regurgitation. Forty-seven of the 74 had pulmonary valve involvement and in this subset 83% had pulmonary regurgitation and 53% had pulmonary stenosis.

The spectrum of cardinoid heart disease also includes left-sided valvular involvement, myocardial metastases, and pericardial effusion. Combined 2-D echo and Doppler examination should be made in all patients when the carcinoid syndrome is initially diagnosed. If asymptomatic disease involving one or more valves is detected, a repeat study should be performed at 6–12-month intervals or when clinically indicated.

Surgical considerations

Surgical removal of a carcinoid tumor is often curative when the disease is detected at an early stage, and surgery may provide significant palliation for selected patients with metastatic disease. It is very important to consider abdominal exploration in the patient with symptoms suggestive of intermittent partial small bowel obstruction since resection, or at the very least, bypass, of the obstructing segment may provide significant palliation. If resection of the primary and the regional nodal metastases is surgically feasible, this should be done to prevent the desmoplastic reaction in the surrounding mesentery. The pathogenesis of the mesenteric fibrosis is not well understood, but the inexorable progression of this process may lead to intestinal ischemia and intestinal angina as well as kinking, stenosis or obstruction of the intestine.

Cytoreductive hepatic surgery

Less than 10% of patients with carcinoid tumors whom we see in the medical oncology division have metastatic disease sufficiently localized to be considered for resection of hepatic metastases, either palliative or curative. Debulking surgery is appealing since these tumors usually have an indolent course and may produce incapacitating symptoms from excess hormone production. Palliative resection should be considered only when at least 90% of the tumor bulk can be excised safely. In our series all 12 patients who survived palliative resection for hormonal symptoms achieved significant relief of symptoms. One patient died within 30 days of surgery of a cerebrovascular accident.

In our series there were 10 curative resections (no gross residual tumor) for metastatic carcinoid tumors; 6 patients had symptomatic endocrinopathies and 4 patients had symptoms caused by the primary tumor. Five of the 6 patients with symptomatic endocrinopathies obtained complete relief of symptoms and are alive at 6–92 months. All four patients with symptoms caused by the primary tumor obtained complete relief; three are alive with no evidence of disease at 8–82 months and the other patient died of progressive disease after 5 years.

Our experience suggests that curative surgery should be considered in all patients with completely resectable metastatic disease and that palliative surgery should be offered to selected patients with metastatic disease since it delays and may reduce the subsequent need for medical therapy (2).

Surgical management of carcinoid heart disease

Carcinoid heart disease should be suspected in patients with the carcinoid syndrome when they develop signs or symptoms of right-sided heart failure. Ideally, we should diagnose these patients before valvular dysfunction leads to diastolic overload and a decrease of functional aerobic capacity. The indication for cardiac surgery and its timing in the patient with carcinoid heart disease is in an evolutionary stage since our treatments for metastatic disease have improved their prognosis. The patients most likely to benefit from cardiac surgery are those with a worsening cardiac status but with an indolent course and relatively stable hepatic metastases.

Only a minority of patients with carcinoid heart disease require a cardiac operation. Patients with mild and stable cardiac symptoms or those with rapidly deteriorating multiorgan disease should not be offered an operation. We have reported on the first 10 patients treated surgically at our institution for carcinoid heart disease. All ten patients underwent tricuspid valve replacement with a mechanical prosthesis. Pulmonary valvectomy was performed in 9 patients and pulmonary valve replacement with a pulmonary homograft was performed in one. The 30-day mortality was 10% and the late mortality was 30%. The remaining 6 patients were alive 4 months to 4 years postoperatively (3).

Symptomatic patients who have carcinoid heart disease and whose metastatic malignant disease is not an imminent threat to life should be offered valve replacement. Operating soon after the onset of increasing cardiac symptoms, before there is deterioration of right ventricular function, will optimize the potential benefit.

Medical therapy

Cyproheptadine

Sixteen patients with metastatic neuroendocrine tumors and the malignant carcinoid syndrome were treated with cyproheptadine at maximum tolerable doses that ranged from 12 to 48 mg daily. Usual side-effects were mild sedation and dry mouth, but three patients found it impossible to sustain treatment due to nausea and vomiting. Most patients had significant relief of diarrhea, frequently associated with weight gain. Relief of flushing was uncommon. The therapeutic benefit produced by cyproheptadine appears to be a peripheral effect because 5-HIAA excretion in these patients was not reduced. Although there have been case reports of objective tumor regression with cyproheptadine therapy, this was not observed in any of these 16 patients (4).

Interferon

Twenty-seven patients with metastatic carcinoid tumor, 24 of whom had the malignant carcinoid syndrome, were treated with recombinant leukocyte A interferon at a planned dose of 24×10^6 U/m^2. Twenty percent of patients with measurable tumor experienced an objective regression and 39% of those with the carcinoid syndrome experienced a reduction by more than 50% in urine 5-hydroxyindoleacetic acid excretion. Flushing was not partially or completely relieved in 65% of patients and diarrhea was relieved in 33%. These favorable treatment effects were transient in nature, with objective regressions persisting for a median of only 7 weeks and hormonal responses for a median of only 4 weeks (5).

Etoposide and cisplatin

Forty-five patients with metastatic neuroendocrine tumors were treated with a regimen of etoposide 130 mg/m^2/day for three days plus cisplatin 45 mg/m^2/day on days 2 and 3 (6). Both drugs were given by continuous intravenous infusion. There were 27 patients with well-differentiated carcinoid tumors or islet cell carcinomas and we observed only two partial objective tumor regressions (7% regression rate). Among 18 patients prospectively classified as having anaplastic neuroendocrine carcinomas, however, there were 9 partial regressions and 3 complete regressions, an overall regression rate of 67%.

Hepatic arterial devasculatization and chemotherapy

Sixty-four symptomatic carcinoid patients with measurable hormonal and/or tumor parameters and proven hepatic dominant metastatis have been treated with hepatic artery occlusion, either by surgical ligation or by percutaneous embolization. In 23 patients no further treatment was given and in 41 patients they were started three weeks later on decarbazine (DTIC) (250 mg/m^2 × 5 days) plus doxorubicin (50 mg/m^2 i.v.), alternating every 4–5 weeks with 5-fluorouracil (400 mg/m^2 × 5 days) plus streptozotocin (500 mg/m^2 × 5 days).

In the 23 patients treated with hepatic artery occlusion alone the regression rate was 65% with the median duration of regression being 6.4 months. In the 41 patients treated with sequential hepatic artery occlusion followed by chemotherapy the regression rate was 80% and the median duration of regression was 18 months. The results with this program appear to show more frequent, more complete, and more lasting responses than in our prior experience with either hepatic artery occlusion or chemotherapy used alone (7).

Somatostatin analogue therapy

Octreotide, the octapeptide analogue of native somatostatin, has a half-life of 2–3 h after subcutaneous administration. We first started studying the drug in 1984 when it was code named SMS 201-995. The relief of flushing, diarrhea, and wheezing was so impressive that in 1988 it was approved by the FDA and marketed as Sandrostatin. The first 66 patients with the malignant carcinoid syndrome were treated with chronic somatostatin analogue therapy using doses ranging from 150 to 500 μg administered subcutaneously t.i.d. (8, 9). Overall, flushing responded in 87%, diarrhea in 77% and a major (≥50%) reduction in 5-HIAA was seen in 77%. In 23 patients with measurable tumor masses the objective tumor regression rate, as assessed by standard oncologic criteria, was 17%. As shown in the Figure, the median survival for the 66 patients receiving chronic somatostatin analogue therapy is 3 years. The survival in this cohort of patients is substantially longer than was seen previously in 92 patients treated with chemotherapy on an ECOG trial (7–12 months) (10). The majority of the somatostatin-treated patients had already received one or more cytotoxic chemotherapy regimens. Even though objective tumor regression was unusual, previously progressive disease often became stable and this seems to have been translated into the favorable long-term survival.

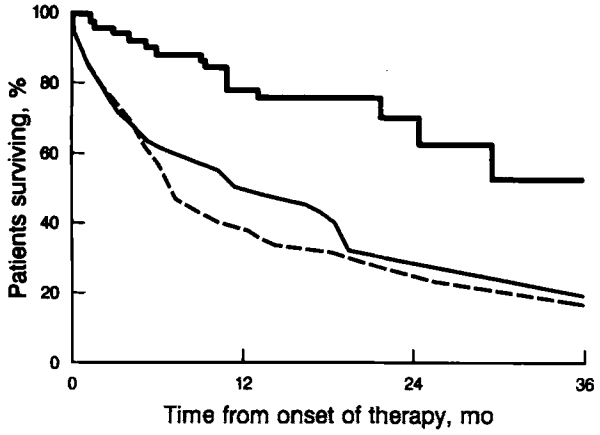

Figure. Survival curves of patients with metastatic carcinoid tumors treated with the somatostatin analogue, octreotide, compared to historical controls who were randomized to one of two combination chemotherapy regimes on an Eastern Cooperative Oncology Study. ——— somatostatin (n = 66); —— streptozotocin + CTX (n = 48); --- streptozotocin + 5-FU (n = 44).

ACKNOWLEDGEMENT

This work was supported in part by grant No. CA 31224 from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

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