Chemotherapy of Metastatic Carcinoid and Islet Cell Tumors

A Review

LARRY K. KVOLS, M.D.
MARTIN BUCK, F.R.A.C.P.
Rochester, Minnesota

The concept of a single unifying cell of origin for tumors of widely separate sites of origin but similar cytochemical and ultrastructural properties is recognized as that of the APUD (Amine Precursor Uptake and Decarboxylation) cell theory [1]. These APUD cells are thought to be the origin of tumors such as carcinoids, chemodectomas, ganglioneuroblastomas, islet cell carcinomas of the pancreas, medullary carcinomas of the thyroid, melanomas, neuroblastomas, paraganglionomas, pheochromocytomas, and small cell carcinomas of the lung [2]. This cytologic basis of cell similarity has enabled investigators to use similar treatment programs for tumors of great anatomic diversity.

The different biologic behavior of metastatic endocrine tumors often requires a unique approach to therapy. For example, aggressive treatment should not be used in patients in the early stages of metastatic carcinoid if they have no tumor symptoms or only minor symptoms from the carcinoid syndrome. Symptoms that significantly interfere with daily activities and are not amenable to therapy with ordinary measures represent one indication for chemotherapy. The development of one of the unfavorable prognostic signs, such as 5-hydroxyindoleacetic acid (5-HIAA) excretion of more than 150 mg per 24 hours or the presence of carcinoid heart disease, would be another indication [3]. Similarly, in many patients with endocrine hypersecretion syndromes from metastatic islet cell carcinoma, treatment with cytotoxic chemotherapy can be withheld until symptoms resistant to pharmacologic maneuvers develop, or if rapidly progressive disease supervenes. The distressingly low levels of antitumor activity with combination chemotherapy against some of these tumors make it necessary to carefully weigh the potential benefits of therapy against unwarranted toxicity resulting from therapy.

Another unique problem associated with the treatment of these tumors with chemotherapy has been the lack of a consistent definition of response to therapy. The presence of a tumor product in serum or urine has enabled investigators to detect reductions in secretion of these substances without necessarily observing objective regression of tumor masses. Often, these decreases in tumor products are associated with symptomatic improvement and therefore are important. In the past, many chemotherapeutic trials did not have rigid response criteria, and any tumor shrinkage or decline in tumor secretion was interpreted as a response; consequently, overly enthusiastic therapeutic results sometimes appeared in the literature. We are now able to measure accurately serum levels of most gastroenterohepatic hormones, calcitonin, and neuropeptides to determine the pattern of tumor secretion and to define a complete response to therapy. With the current emphasis on biochemical markers of disease activity, a 50 percent or greater drop in the serum or urine

From the Division of Medical Oncology, Department of Oncology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The material in this review was part of an article submitted to *Seminars in Oncology*, which is in press. Requests for reprints should be addressed to Dr. Larry K. Kvols, Division of Medical Oncology, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905.

TABLE I Single-Agent Chemotherapy for Carcinoid Tumors

Agent	Patients	Objective Response: Number (percent)	Reference
Doxorubicin	33	7 (21)	[3]
5-Fluorouracil	19	5 (26)	[3]
Dacarbazine	15	2 (13)	[7]
Actinomycin D	17	1 (6)	[7]
Cisplatin	15	1 (7)	[9]

TABLE II Streptozotocin-Based Combination Chemotherapy Regimens for Carcinoid Tumors

Regimen	Patients	Objective Response: Number (percent)	Reference
Streptozotocin* + 5-fluorouracil	43	14 (33)	[3]
Streptozotocin + cyclophosphamide	47	12 (26)	[4]
Streptozotocin† + 5-fluorouracil	80	18 (23)	[18]
5-Fluorouracil + doxorubicin + cyclophosphamide + streptozotocin	20	7 (35)	[20]
Streptozotocin (weekly) + doxorubicin	10	4 (40)	[19]

*Streptozotocin in five-day courses repeated every six weeks.
†Streptozotocin in five-day courses repeated every 10 weeks.

marker hormone level is sometimes considered a response, whether or not there has been a decrease in the size of measurable lesions.

METASTATIC CARCINOID

Initial reports by Moertel [3] on chemotherapy in carcinoid used 5-fluorouracil at a dose of 500 mg/m^2/day in five-day courses given every five weeks; objective responses were observed in five of 19 patients. Using the same dose and schedule, an identical response rate of 18 percent was observed in 11 patients in a multi-institutional trial done by the Eastern Cooperative Oncology Group (ECOG) [4]. Two separate studies of an anthracycline antibiotic, doxorubicin, given at a dose of 60 mg/m^2 every three to four weeks, have reported objective responses in 21 percent of patients [3,5].

Reports of other active single agents include the observation by Kessinger's group [6] of objective improvement lasting for a year in one patient and subjective improvement in another patient treated with dacarbazine. In a Mayo Clinic trial, two of 15 partial responses were observed using the same agent [7]. Nearly two decades ago, actinomycin D was reported to have caused improvement in three of five carcinoid patients [8]. The report of Van Hazel and co-workers was less encouraging, with only one of 17 patients showing a response to actinomycin D, but it is of interest that the patient with a response to actinomycin D has had remarkable clinical improvement lasting more than eight years [7]. Fifteen patients with metastatic carcinoid tumor were treated with cisplatin at doses ranging from 45 to 90 mg/m^2 administered by rapid intravenous infusion, and this treatment was repeated every three to four weeks [9]. Only one patient (7 percent) showed any evidence of tumor regression; regression was only partial and lasted only 3.5 months. It is unlikely that cisplatin given in this dose and schedule as a single agent has any therapeutic potential in carcinoid tumors. Single-agent chemotherapeutic experiences are summarized in **Table I**.

The nitrosourea antibiotic streptozotocin was observed to induce diabetes mellitus in preclinical toxicologic studies [10]. This unique pattern of toxicity translated into significant activity against islet cell carcinomas and led to trials in patients with other neuroendocrine tumors. In six patients with carcinoid who received streptozotocin, Moertel [3] reported one objective regression and two mixed responses with regression of some lesions and progression of others. Two other reports also identified antitumor activity for this agent [11,12], but Schein et al [13] found no responses among eight patients.

Mengel and Shaffer [14] reported responses in six of 11 patients treated with the combination of cyclophosphamide plus methotrexate. This treatment was one of the early reports of enhanced activity with combination drug therapy in carcinoids and was accepted as standard therapy for this disease for several years. Using more rigid response criteria, the Mayo group failed to observe a single response in 16 patients reported in 1984 [15].

In 1975, Moertel [16] first reported responses in six of nine carcinoid patients using the combination of 5-fluorouracil plus streptozotocin. Later in that decade, Chernicoff et al [17] reported responses in four of 10 carcinoid patients treated with the same regimen. The combination of 5-fluorouracil plus streptozotocin was one of the treatment arms in a randomized multi-institutional trial performed by investigators in the ECOG [4]. That randomized trial compared 5-fluorouracil plus streptozotocin versus cyclophosphamide plus streptozotocin. The objective response rates were 33 and 26 percent, respectively (**Table II**). Although a somewhat more favorable response rate was found with the 5-fluorouracil and streptozotocin combination, this difference was not statistically significant, nor were there differences in duration of response, interval to progression, or survival. Response rates were more favorable in patients with a documented carcinoid syndrome and those with a better performance status. It was

interesting that with both regimens, the response rate was significantly greater for small bowel carcinoids than for carcinoids of pulmonary or unknown origin.

The next ECOG protocol used streptozotocin given every 10 weeks, rather than every five weeks, in an attempt to decrease anorexia, nausea, and vomiting; 5-fluorouracil was still given daily for five days every five weeks [18]. The second treatment arm in this randomized trial was single-agent doxorubicin, 60 mg/m^2 intravenously once each month. Unfortunately, nausea and vomiting secondary to streptozotocin therapy were not attenuated, but the response rate seemed to be, with only 18 of 80 patients (23 percent) fulfilling the criteria for response. The response rate for doxorubicin in this protocol was 17 of 81 (23 percent). The median duration of response was 26 weeks for doxorubicin and 31 weeks for the combination. In contrast to the preceding ECOG study, the location of the primary tumor did not correlate with the likelihood of survival.

A weekly schedule of streptozotocin given with doxorubicin in a single institution has been reported to cause regressions in four of 10 carcinoids [19]. A four-drug regimen comprised of 5-fluorouracil, streptozotocin, doxorubicin, and cyclophosphamide does not appear to offer any clear-cut therapeutic advantage with seven of 20 (35 percent) patients showing a response [20].

Other treatment approaches using non-chemotherapeutic agents such as cyproheptadine have been reported to produce tumor regression, but confirmation of these observations is still pending [21]. Tamoxifen was also reported to produce symptomatic control of the carcinoid syndrome and, subsequently, evidence of objective remission [22,23]. A collaborative trial to confirm this activity failed to note any tumor regression or improvements in 5-HIAA levels [24]. A report by Oberg and associates [25] at the University of Upsala has sparked interest in using interferon for the carcinoid syndrome. Their six patients had significant symptomatic improvement and some reduction in 5-HIAA excretion.

Martin and colleagues [26] have described eight patients with the carcinoid syndrome at our institution who underwent hepatic artery ligation at the time of laparotomy. The advantage of the surgical approach is that it permits resection of the frequently obstructive ileal primary lesions; this was necessary in five of the six patients with small-bowel primaries. Facial flushing ceased in all patients and diarrhea was uniformly reduced at the time of hospital discharge. All patients became febrile and had striking increases in the serum glutamic-oxaloacetic transaminase values during the first postoperative week, but showed quick recovery thereafter. The duration of response ranged from three to 10 months (median, five months). Other investigators have confirmed that hepatic artery occlusion alone is an effective means of inducing tumor debulking for this disease [27–29]. Because vascular occlusion-induced hepatic dysfunction is transient, the vascular occlusion does not preclude future chemotherapy.

The early results of the Mayo Clinic trial of sequential hepatic artery occlusion and chemotherapy for metastatic carcinoid tumor have been reported previously [30]. Ten symptomatic patients with measurable hormonal and/or tumor parameters and proven hepatic dominant metastases have been treated with hepatic artery occlusion either by surgical ligation or percutaneous embolization. Three weeks later, therapy was started with dacarbazine, 250 mg/m^2 for five days, plus doxorubicin, 60 mg/m^2 intravenously, alternating every four weeks with 5-fluorouracil, 400 mg/m^2 for five days, plus streptozotocin, 500 mg/m^2 for five days. Nine of the ten patients had striking or complete relief of the carcinoid syndrome, with urinary 5-HIAA elevations reduced from 63 to 100 percent. The remaining patient had minor improvement for 12 months. Hepatic artery occlusion had side effects as noted in the earlier study. Chemotherapy produced its anticipated side effects, primarily vomiting and leukopenia. The early 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. This prospective trial remains in progress.

Somatostatin is a ubiquitous hormone that inhibits the release of numerous peptides such as growth hormone, insulin, glucagon, and gastrointestinal peptides [31]. Native somatostatin has been reported to be effective in blocking the carcinoid flush induced by pentagastrin and in controlling other symptoms associated with the carcinoid syndrome [32,33]. These initial observations had limited therapeutic application, because the short half-life of the native compound required continuous intravenous infusion. An analogue of somatostatin with eight amino acids rather than 14 was synthesized and reported to be more specific, potent, and longer acting in its inhibitory effects [34].

Our initial experience with this longer-acting analogue of somatostatin (SMS 201-995) was very favorable in terms of ameliorating symptoms related to neuroendocrine tumors [35]. We have now studied the long-term administration of this analogue in 25 patients with histologically proven metastatic carcinoid tumor and the carcinoid syndrome. The drug was self-administered by subcutaneous injections at a dose of 150 μg three times daily. Flushing and diarrhea associated with the syndrome were promptly relieved. All 25 patients had elevated 24-hour urine 5-HIAA excretions to serve as an objective indicator of disease activity (mean, 265 mg per 24 hours; range, 14 to 1,079 mg per 24 hours). Eighteen of the 25 patients (72 percent) have had a 50 percent or greater decrease in their 5-HIAA level compared with their pretreatment level. The median duration of this biochemical response is 12+

TABLE III Chemotherapeutic Experience in Islet Cell Carcinoma

Regimen	Patients	Objective Response: Number (percent)	Reference
Streptozotocin	17	7 (41)	[39]
Doxorubicin	20*	4 (20)	[41]
Chlorozotocin	13†	7 (53)	[42]
Streptozotocin + 5-fluorouracil	40	25 (63)	[40]

*Previously treated patients.
†Patients who had not previously received chemotherapy.

TABLE IV Treatment Schema for ECOG Randomized Study of Islet Cell Carcinoma

Treatment Arm	Regimen
Group A	5-Fluorouracil (400 mg/m^2 on Days 1 through 5, every 6 weeks) Streptozotocin (500 mg/m^2 on Days 1 through 5, every 6 weeks)
Group B	Doxorubicin (50 mg/m^2 on Day 1, every 3 weeks) Streptozotocin (500 mg/m^2 on Days 1 through 5, every 6 weeks)
Group C	Chlorozotocin (150 mg/m^2 on Day 1, every 7 weeks)*

*If their disease progresses, chlorozotocin-treated patients are randomly assigned to either treatment arm A or B.

months (range, one to 18+ months). There has been no evidence of renal, hepatic, neurologic, or hematologic toxicity. We have previously reported one instance in which therapy with this somatostatin analogue promptly reversed a potentially lethal carcinoid crisis occurring with the induction of anesthesia [36].

At this point in time, combination chemotherapy for metastatic carcinoid has not been clearly shown to have any major advantage compared with single-agent chemotherapy and continues to be a challenge to clinicians. Newer modalities such as hepatic artery occlusion, interferons, and use of somatostatin analogues offer some promise, but all treatment of this nature should be considered an experimental endeavor.

ISLET CELL CANCER OF THE PANCREAS

During early trials, the effectiveness of 5-fluorouracil in pancreatic islet cell cancer was found to be similar to that in other gastrointestinal malignancies [4]. It was not until the observation that streptozotocin induced selective pancreatic beta-cell damage that a chemotherapeutic agent was identified that appeared to have specificity for metastatic pancreatic islet cell cancer. The first report of clinical effectiveness of streptozotocin for this condition came from Murray-Lyon and colleagues [37] in 1968; following that report, many anecdotal reports appeared suggesting the efficacy of streptozotocin in this disease. Subsequently, a large series compiled by Broder and Carter [38] from the National Cancer Institute confirmed the activity of streptozotocin in pancreatic islet cell cancer. In this series, 37 percent of patients with measurable disease had an objective regression (greater than 50 percent reduction), and 54 percent of functional tumors had at least a 50 percent decline in biochemical parameters. At that time, there was no consensus on the dosage or schedule of administration of streptozotocin, and this series contained various methods of administration. Also, the toxicity of streptozotocin was often formidable, with frequent severe nausea and vomiting combined with less commonly encountered nephrotoxicity and hepatotoxicity.

In 1971, investigators at the Mayo Clinic reported on the effectiveness of an intensive five-day administration schedule of streptozotocin, and this regimen was generally accepted as the standard mode of therapy [39]. Because of the lack of myelosuppression with this drug, combination with other agents appeared feasible, and early reports suggested an increased level of antitumor activity when combined with 5-fluorouracil [4]. A prospective, randomized study by the ECOG published in 1980 compared streptozotocin alone with the combination of streptozotocin and 5-fluorouracil [40]. The combination had advantages over streptozotocin alone in overall rates of response (63 versus 36 percent) and in the frequency of complete responses (37 versus 12 percent). The median duration of response was 17 months for all patients, and there was no apparent difference in the response of the various hormone-producing tumors. Although not statistically significant, those patients treated with the combination survived a median of 26 months, compared with 16.5 months for the single drug. Once again, toxicity was significant, with nausea and vomiting in more than 80 percent of patients, nephrotoxicity in 30 percent, and a single case of fatal hepatotoxicity. The drug combination was associated with more leukopenia (73 versus 5 percent), and there was one treatment-related death due to sepsis. This study confirmed the effectiveness of streptozotocin and 5-fluorouracil combinations but also indicated a need for ongoing studies to identify less toxic, equally active programs.

Other combinations of streptozotocin have been used, and Kelsen et al [19] have reported a program of weekly streptozotocin and doxorubicin therapy whereby one of five patients with pancreatic islet cell carcinoma had an objective remission. Since this treatment was associated with only minor myelosuppression, the dosage of doxorubicin was to be escalated in future trials to try to improve the response rate. Use of doxorubicin alone has also been

TABLE V Dacarbazine Regimens in Islet Cell Carcinomas

Dacarbazine Regimen	Patients*	Objective Response†	Response Duration (months)	Reference
250 mg/m^2 for 5 days	1	1	22+	[43]
250 mg/m^2 for 5 days	1	1	30+	[44]
300 mg/m^2 for 5 days	1	1	3+	[45]
250 mg/m^2 for 5 days	2	2	22,24+	[46]
250 mg/m^2 for 5 days	5	4	3+,7+,7+,10+	[47]
250 mg/m^2 for 5 days‡	5	4§	9+,14+,40+,48	[6]
100 mg/m^2 for 5 days**	1	1	2+	[48]

*All except two patients had malignant glucagonomas.
†Response required at least a 50 percent drop in circulating hormonal levels or a reported 50 percent or greater decrease in measurable tumor.
‡Two patients were treated with 850 mg/m^2 or 1 g intravenously every 28 days.
§Non-responder had a non-functional pancreatic islet cell tumor that remained stable for three years.
**Dosage was later increased to 300 mg/m^2 for five days.

reported to have definite activity, with four of 20 responses in previously otherwise-treated patients [41]. **Table III** delineates these chemotherapeutic experiences in patients with pancreatic islet cell carcinoma.

A current ECOG study (**Table IV**) is comparing the use of streptozotocin plus 5-fluorouracil with streptozotocin plus doxorubicin and with the new nitrosourea, chlorozotocin. The latter agent is a drug structurally similar to streptozotocin, with considerably less gastrointestinal toxicity but increased myelosuppression. Chlorozotocin can be given at full doses on a single day every six to seven weeks, whereas streptozotocin needs to be given over five days; also, chlorozotocin appears to have less potential for nephrotoxicity. This drug has been evaluated in a phase II trial by the Southwest Oncology Group. Among 17 patients with pancreatic islet cell carcinoma receiving either 200 mg/m^2 or 100 mg/m^2 every six weeks, there were two complete and five partial responses [42]. No responses were observed among the four previously treated patients, suggesting a similar mechanism of action and cross resistance to streptozotocin. If antitumor activity of equal degree as streptozotocin is confirmed with chlorozotocin, then improved tolerance may make the latter drug the preferred nitrosourea in metastatic pancreatic islet cell carcinoma.

In 1979, Kessinger and colleagues [43] identified dacarbazine as an effective drug in the treatment of malignant glucagonoma resistant to streptozotocin. Their report was followed by several isolated reports confirming activity of dacarbazine in untreated and a few previously treated patients with metastatic malignant glucagonoma [44–48]. In 1983, Kessinger et al [6] expanded their experience to include five additional patients with pancreatic islet cell carcinoma among a series of patients with APUD tumors treated with dacarbazine. In this group, there was one complete tumor regression, as well as one complete and two partial biochemical remissions. Almost all reported responding cases of pancreatic islet cell carcinoma treated with dacarbazine are malignant glucagonomas (**Table V**). This high level of response possibly represents some reporting bias. Nevertheless, this activity has prompted some authors to recommend dacarbazine as the drug of choice for malignant glucagonoma [6,46–48]. A prospective trial of this agent in patients with pancreatic islet cell carcinoma is being done by the ECOG at this time.

Anecdotal reports of other chemotherapeutic agents used in pancreatic islet cell carcinoma have been less encouraging. A single response to actinomycin D and steroids has been reported, whereas etoposide (VP-16) has been found to be ineffective in a report of two patients [49,50]. The combination of doxorubicin and cisplatin used in patients with APUD tumors resulted in two minor responses lasting 52 and 23 weeks in patients with pancreatic islet cell carcinoma [51]. Experience with cisplatin alone is limited, and further studies are needed to identify its level of antitumor activity for islet cell carcinoma.

Experience with hepatic artery occlusion in pancreatic islet cell carcinoma is much less than with carcinoid tumors but has shown early promise. Moertel and colleagues [30] have treated three functioning pancreatic islet cell carcinomas with hepatic artery occlusion followed by chemotherapy. All patients have had dramatic hormonal responses; two patients have had striking tumor regressions. Two patients with non-functional tumors have had only minor improvements [30].

Somatostatin analogues have been shown to have some very exciting applications in the treatment of the plethora of endocrine manifestations of pancreatic islet cell carcinoma affecting the function of the gastrointestinal tract [52,53]. Long and colleagues [54] reported their initial experience with an analogue of somatostatin in the treatment of eight patients with a variety of islet cell tumors and found striking inhibition of insulin and glucagon secretion.

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