Treatment of Neuroendocrine Carcinomas With Combined Etoposide and Cisplatin

Evidence of Major Therapeutic Activity in the Anaplastic Variants of These Neoplasms

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Forty-five patients with metastatic neuroendocrine tumors were treated with a regimen of etoposide 130 mg/m²/d for 3 days plus cisplatin 45 mg/m²/d on days 2 and 3. Both drugs were given by continuous intravenous infusion. Among 27 patients with well-differentiated carcinoid tumors or islet cell carcinomas, only two partial objective tumor regressions were observed (7%). Among 18 patients prospectively classified as having anaplastic neuroendocrine carcinomas, however, there were nine partial regressions and three complete regressions, an overall regression rate of 67%. For anaplastic disease, the median duration of regression was 8 months (range to 21 months). Tumor response was unrelated to primary site, endocrine hyperfunction, or prior therapy experience. The median survival of all patients with anaplastic tumors was 19 months; this seemed favorable when considering the small experiences with these rare tumors reported in the literature. Toxicity, which was severe for most patients, consisted primarily of vomiting, leukopenia, thrombocytopenia, anemia, alopecia, and neuropathy. The anaplastic neuroendocrine tumor is strongly responsive to therapy with combined etoposide and cisplatin. Patients with undifferentiated carcinomas, originating in typical neuroendocrine tumor sites (small and large bowel, pancreas, and stomach) or of unknown origin, who have consistent histologic findings by light microscopy should be evaluated for this possibility with appropriate immune staining or electron microscopy. *Cancer* **68:227–232, 1991.**

ISLET CELL CARCINOMAS and carcinoid tumors are a special challenge to medical management because they are rare, and therefore, sufficient patient numbers are not available to conduct the large-scale Phase II trials used to screen new treatment regimens for activity in the more common malignant diseases. Ideas for research trials in carcinoid and islet cell carcinoma patients are, therefore, often taken from clinical success in more frequently encountered cancers. Certainly the most attractive of these would be other cancers derived from neuroendocrine cells, *i.e.*, cells with secretory granules and the capability of producing polypeptide hormones or biogenic amines. These cells occur in various locations, such as the base of the crypts of Lieberkuhn in the appendix and small intestine, the islets of Langerhans in the pancreas, and the granular basal layer of the bronchial epithelium. The most common cancer derived from neuroendocrine cells is the small cell carcinoma of the lung.

Several chemotherapeutic regimens are effective in treating small cell lung cancer, not only in producing frequent objective tumor regressions but also in extending patient survival. Probably the most common of these regimens in modern use are those involving a combination of etoposide and cisplatin. This fact led us to the hypothesis that the activity of etoposide plus cisplatin in small cell carcinoma of the lung could predict activity in the less common neuroendocrine tumors, *i.e.*, the carcinoid and the islet cell carcinoma. In addition, Davis *et al.*[1] reported activity with this combination in a small group of carcinoid tumor patients.

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Major differences between the small cell carcinoma and the carcinoid or islet cell carcinoma are that small cell lung cancer has highly anaplastic histologic findings and an aggressive clinical course whereas carcinoids and islet cell carcinomas usually are well differentiated and have a characteristically indolent course. In the spectrum of neuroendocrine neoplasms, there is a group of tumors best described as anaplastic neuroendocrine carcinomas. These tumors histologically show a less well-developed neuroendocrine pattern and have greater cytologic atypia than carcinoid tumors or islet cell carcinoma. In addition, they have greater mitotic activity and small foci of necrosis frequently are present. These anaplastic neuroendocrine carcinomas lack the extensive sheet-like necrosis commonly identified in small cell undifferentiated carcinomas. In our experience, this histologic finding is associated with more rapid advance of malignant disease and less frequent clinically recognizable excess hormone production. Because the anaplastic neuroendocrine tumors bear a closer histologic resemblance to small cell lung cancer than do the typical carcinoid or islet cell carcinoma, we also hypothesized that these anaplastic tumors might be particularly vulnerable to etoposide plus cisplatin treatment.

The particular etoposide and cisplatin schedule we chose for study involved a 3 day regimen with each agent given by 24-hour intravenous infusion. It was our hope that continuous exposure of cancer cells to cisplatin and etoposide could enhance the therapeutic interaction of these two agents. A previous pilot study of this regimen showed that 14 of 15 patients with small cell lung cancer had tumor regressions although several of these patients were treated with suboptimal doses of etoposide and several had extensive disease.[2]

Materials and Methods

Patient Selection

All patients selected for study had histologic confirmation of metastatic neuroendocrine tumor. Before study entry, the patients were classified as having a well-differentiated carcinoid tumor, a well-differentiated islet cell carcinoma, or an anaplastic neuroendocrine tumor. Those classified as carcinoids had either an identified primary in a typical location (small bowel, appendix, rectum, stomach, or lung) or an elevation of urine 5-hydroxyindoleacetic acid (5-HIAA) excretion and a normal pancreas on either abdominal exploration, computed tomographic scan (CT), or ultrasound examination. Appropriate evidence for assuming islet cell carcinoma was confirmation of a primary tumor in the pancreas by abdominal exploration, CT scan, or ultrasonography. In the absence of clear evidence of such a primary tumor, islet cell carcinoma was assumed clinically if the patient had distinct elevation of any of the hormonal substances characteristically produced, *e.g.*, gastrin, glucagon, vasoactive intestinal peptide, or insulin. All patients classified as having an anaplastic neuroendocrine tumor were so designated by a Mayo Clinic pathologist after review of the histologic material. In each instance, this classification was made before study entry, not after the fact. This distinction was clear, and no tumor was classified as "moderately undifferentiated." It was required that each patient have either measurable tumor or definite hormonal abnormalities or both to serve as indicators of response to therapy. The following were accepted as evidence of measurable tumor: (1) a clearly demarcated tumor area which was bidimensionally measurable with a ruler or caliper on physical examination or chest radiography, (2) a clearly defined perfusion defect on radioisotope liver scan or a tumor area on CT scan, either of which must measure at least 5 cm in greatest diameter, or (3) malignant hepatomegaly with a clearly defined liver edge extending at least 5 cm below the xiphoid or costal margin on quiet respiration. If hormonal abnormalities only were used as indicators of response, it was required that pretreatment values be at least twice the upper limits of normal. If 24-hour urine 5-HIAA excretion was used, it was required that the pretreatment value be at least 20 mg (normal, $\leq$ 6 mg). It was also required that these abnormal values be found on two consecutive determinations obtained within 2 weeks before study entry. The following were contraindications to study entry: leukopenia ($< 4000/\mu l$), thrombocytopenia ($< 100{,}000/\mu l$), an Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4 (unless disability was caused solely by a hormonal syndrome), uncontrolled infection, immunotherapy, or chemotherapy during the preceding 3 weeks, any prior therapy with either etoposide or cisplatin, and a serum creatinine greater than 1.5 mg/dl.

Treatment Method

Before therapy, and also at the time of each evaluation, a medical history was taken, and the patient underwent physical examination and tumor measurements. Laboratory analysis included leukocyte count, platelet count, hemoglobin, a blood chemistry panel, and assays of hormonal indicators. Appropriate imaging was obtained of any indicator lesions, as was chest radiography, pretreatment and at every other posttreatment evaluation.

Therapy was administered in the hospital. Etoposide was administered by continuous infusion in a solution of 5% dextrose and 0.45% saline. The dose was 130 mg/m^2 given daily for 3 consecutive days. Cisplatin was given in the same infusion at a dose of 45 mg/m^2 on days 2 and 3 of etoposide administration. Appropriate antiemetics were administered with each course of therapy. Courses were repeated every 4 weeks with reductions in dose if

excessive toxicity was experienced during the preceding course. Therapy was continued until tumor progression, or in the case of stable disease or tumor regression, as long as there was no evidence of symptomatic or general deterioration, and the therapy was tolerable clinically.

All patients were evaluated for therapeutic response before initiation of their next course of therapy. Patients were declared to have had a complete regression if there was total disappearance of all clinically detectable tumor and return of all abnormal hormonal indicators to normal range. Partial regression was defined as a greater than 50% reduction in the products of the longest perpendicular diameters of lesions measured by either physical examination or imaging. If malignant hepatomegaly was the indicator, it was required that there be more than a 30% decrease in the sum of distances below the costal margin. To declare a hormonal response, it was required that this parameter be reduced to less than 50% of the pretreatment value or to normal range. Time to progression and survival were measured from the time of study entry. Duration of tumor regression was measured from time of entry to the last time regression was documented.

Results

A total of 46 patients, all eligible according to the study criteria, were enrolled between May 1987 and February 1990. A single patient withdrew consent and left the study after only 1 day of therapy. We were unable to obtain any follow-up information on this patient. He therefore was considered not evaluable, and he is not included in any of the following analyses. Among the 45 eligible and evaluable patients, 13 had well-differentiated carcinoid tumors, 14 had well-differentiated islet cell carcinomas, and 18 had anaplastic neuroendocrine tumors. Anaplastic tumors were identified as neuroendocrine by consistent histopathologic findings plus a clinical endocrine syndrome in ten patients, by light microscopy only in one patient,

TABLE 1. Patient Characteristics

Characteristic	Carcinoid tumor	Islet cell carcinoma	Anaplastic neuroendocrine carcinoma
Total no. of patients	13	14	18
Male/female	8/5	7/7	10/8
Median age in yr (range)	61 (52–67)	47 (22–64)	52 (24–74)
Median time from diagnosis of metastasis in mo	28	20	4.5
(Range)	(½–100)	(1–41)	(5 days–41 mo)
Primary tumor			
Pancreas	—	14	6
Small bowel	5	—	2
Lung	2	—	1
Cecum & right colon	3	—	1
Rectum	1	—	2
Stomach	—	—	3
Unknown	2	—	3
Endocrine abnormalities*			
5-HIAA	12	—	5
Gastrin	—	6	2
Glucagon	—	5	1
Insulin	—	3	—
Pancreatic polypeptide	—	2	1
Hypercalcemia	—	2	—
ACTH	—	—	2
None	1	4	9
Prior chemotherapy	9	10	3
Indicators of response*			
Liver tumor	12	11	14
Other tumor	—	3	7
Endocrine marker	12	9	7
Performance score†			
0	4	6	5
1	8	5	7
2	1	3	5
3	—	—	1‡

5-HIAA: 5-hydroxyindoleacetic acid.
* Several patients had more than one endocrine abnormality or indicator of response.
† ECOG performance score: 0 (fully active) to 4 (totally disabled).
‡ Disability caused by endocrine syndrome.

and in seven patients, by light microscopy plus electron microscopy (five patients) and/or immune staining (four patients). In the latter group, two tumors were positive for neuron-specific enolase, two for synaptophysin, and two for chromogranin.

The characteristics of these patients are documented in Table 1. Patients with islet cell carcinomas and anaplastic neuroendocrine tumors were younger than patients with carcinoids. Most had primary tumors in areas typical for neuroendocrine neoplasms. The five patients classified as having tumors of unknown origin had been examined with chest radiography, CT scanning, gastrointestinal imaging procedures, and in one case each, laparoscopy and surgical exploration of the abdomen. Patients with anaplastic neuroendocrine tumors had a much shorter interval from diagnosis of metastatic disease to the onset of therapy, one half of them did not have associated endocrine syndromes, and most had had no prior chemotherapy exposure. Seventy-eight percent of patients entered in this trial had an excellent or good performance score (*ECOG* score, 0 or 1).

Therapeutic Results

Patients with typical well-differentiated carcinoid tumors and islet cell carcinomas were treated with a median of three courses of therapy (range, one to seven courses), whereas patients with anaplastic neuroendocrine tumors were treated with a median of five courses (range, two to 22 courses).

Response to therapy according to the three tumor types is displayed in Table 2. Among the 13 patients with well-differentiated carcinoid tumors, none showed an objective tumor response, reduction in 5-HIAA level, or improvement of their carcinoid syndrome. Eleven patients had stable disease, but the median duration of this stability was only 3 months, and the median interval to progression for all patients was only 3 months.

Among the 14 patients with islet cell carcinoma, two (15%) had partial tumor regressions. Both of these patients had had prior chemotherapy. One of these with a nonfunctioning tumor showed a greater than 50% reduction in abdominal nodal masses displayed by CT scan; this persisted for 4.5 months. The second patient had a greater than 50% reduction in abdominal and liver masses and reduction in gastrin level from 480 to 110 pg. This response persisted for 6 months. It is interesting that one patient with tumor progression and increasing levels of gastrin and glucagon also had complete relief of hyperinsulinism and accompanying intractable hypoglycemia. As with the carcinoid tumor, both duration of stable disease and interval to progression were short: 3 months and 4 months, respectively.

In contrast, 12 of 18 patients (67%) with anaplastic neuroendocrine pathologic findings had objective tumor regression. Three of these tumors regressed completely. In two this was determined by clinical findings and imaging and in one by restaging laparotomy with biopsies of previously involved organs. Regression was evidenced quickly (median, 1 month). The overall median duration of regression was 8 months (range to 21 months). In all instances regression involved reduction in measurable tumor mass. Response was not perceptibly influenced by tumor function. Among seven patients with endocrine response indicators, four had regression. Two of these patients had reduction of elevated 5-HIAA levels to normal range, and one had a 5-HIAA reduction from 311 mg (in 24 hours) to 103 mg. In one patient elevations of both gastrin and glucagon returned to normal. Two of the three patients with prior chemotherapy exposure had partial responses. The median interval to progression for all anaplastic tumor patients was 9 months (range to 21 months).

TABLE 2. Objective Response to Therapy

	Carcinoid tumor (n = 13)	Islet cell carcinoma (n = 14)	Anaplastic neuroendocrine carcinoma (n = 18)
Complete regression	—	—	3 (17%)
Partial regression	—	2 (14%)	9 (50%)
Stable	11	9	6
Progression	2	3	—
Duration of regression*			
Median (mo)	—	5	8
Range (mo)	—	4½ and 6	3–21
Interval to progression*			
Median (mo)	3	4	11
Range (mo)	1–21	1–8	2–21
Survival*			
Median (mo)	10½	15½	19
Range (mo)	3–36+	4–36½+	5–36+

* Estimates: Kaplan–Meier method.

Survival

Twenty-eight of our 45 patients died at a median time of 12.5 months after study entry (range, 3 to 28 months). Seventeen are still living at a median time of 14.5 months (range, 11 to 36.5 months). In Figure 1 we plotted patient survival by the Kaplan-Meier method according to tumor classification and measured from the time of study entry. The median survival for the well-differentiated neuroendocrine tumors was 15 months (carcinoid tumor, 10.5 months and islet cell carcinoma, 15.5 months). Anaplastic neuroendocrine carcinomas showed a modest advantage with a median of 19 months.

Toxicity

Drug toxicity was a major problem for most patients. This frequently required dosage reductions or cessation of therapy. The toxic reactions are documented in Table 3. Nausea and vomiting were frequent despite vigorous antiemetic therapy with metoclopramide, dexamethasone, and other agents. These reactions, however, usually were not severe and did not interfere significantly with patient compliance. Mucocutaneous reactions and diarrhea were relatively minor problems. All patients noted alopecia, usually near complete. Neuropathy, usually sensory and presumably related to cisplatin, was experienced by 24% of patients; in 7%, it was severe. Hearing loss was infrequent. Two thirds of patients had renal toxicity as evidenced by a rising creatinine level. This rise was usually mild (< 2 mg/dl), but one patient had a complete renal shutdown, requiring dialysis for several weeks. A single patient had severe chills and fever with negative blood cultures; we presumed this was a reaction to etoposide. Therapy was not continued in this patient.

Hematologic toxicity was universal. All patients had leukopenia. In five patients, this was life threatening (< 1000/μl), and in three patients, it was complicated by sepsis. Thrombocytopenia was usually mild, but nine patients had counts less than 25,000 μl. No patient hemorrhaged, but one had cutaneous purpura. Thirteen patients had worsening leukopenia and/or thrombocytopenia after repeated courses of therapy. Anemia occurred consistently with repeated courses of therapy and frequently was symptomatic and associated with easy fatigue or exertional dyspnea. There was a definite tendency to increasing anemia with increasing duration of therapy. Overall, most patients had either severe or life-threatening toxicity, but there were no drug-related deaths.

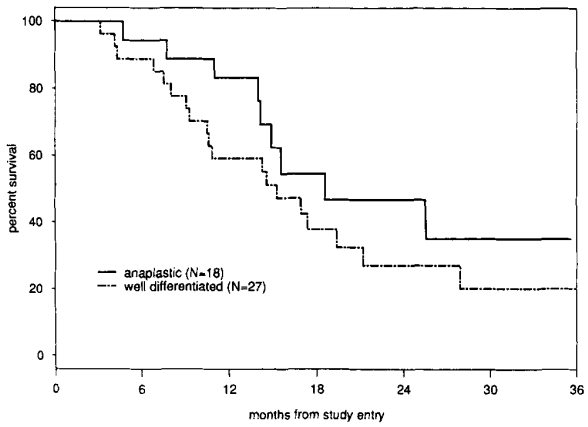

FIG. 1. Comparative survivorship: well-differentiated and anaplastic neuroendocrine tumors.

TABLE 3. Toxic Reactions

Nonhematologic toxicity	Percent of 45 patients	
Toxic reaction	Any	Severe*
Nausea	96	13
Vomiting	93	9
Diarrhea	16	—
Stomatitis	13	2
Neuropathy	24	7
Dermatitis	4	—
Chills & fever	2	2
Hearing loss	2	—
Alopecia	100	100
Renal (↑creatinine)	66	2
Hematologic toxicity		
	Percent of 44 patients†	
Toxic reaction		
Leukopenia (cells/μl)		
< 4000 ≥ 2000	35	
< 2000 ≥ 1000	53	
< 1000	12	
Thrombocytopenia (cells/μl)		
< 130,000 ≥ 50,000	49	
< 50,000 ≥ 25,000	14	
< 25,000	21	
Anemia (fall in g of Hgb)		
≥ 1 < 3	38	
≥ 3 < 4	29	
≥ 4	22	

* Grade 3 or 4 according to NCI Common Toxicity Criteria.
† Adequate counts not obtained in one patient.

Discussion

Our results identify a neoplasm that is highly responsive to chemotherapy. The overall regression rate of 67% with a complete regression rate of 17% found with etoposide and cisplatin therapy of anaplastic neuroendocrine carcinomas was comparable to that in extensive small cell lung cancer. The duration of response was substantive. Although impossible to prove in the absence of a randomized trial, therapy may add to life expectancy in these patients. Their projected median survival was 19 months from the onset of treatment. There is little survival information regarding these patients in the literature, but a median survival of 6 months was reported in a small group

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