5-Fluorouracil, Dacarbazine, and Epirubicin in the Treatment of Patients with Neuroendocrine Tumors

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BACKGROUND. For patients with surgically untreatable neuroendocrine tumors (NETs), the optimal therapeutic approach remains undefined. Somatostatin analogs and interferons have failed to control neoplastic growth, and chemotherapy has been only moderately more effective. The authors' previous study of the combination of 5-fluorouracil (FU), dacarbazine (DTIC), and epirubicin (EPI) (the FDE regimen) documented good tolerability, but the results for tumor growth control were disappointing. In an attempt to improve these results, the authors conducted a preliminary trial of an intensified FDE regimen (FU 500 mg/m^2 administered intravenously [i.v.], DTIC 200 mg/m^2 i.v., and EPI 30 mg/m^2 i.v. on Days 1, 2, and 3 every 3 weeks).

METHODS. Thirty NET patients (15 male, 15 female; median age, 55 years; age range, 19–72 years) were enrolled, none of whom had previously been given chemotherapy. The histologic types of disease were gastroenteropancreatic (GEP) tumors (n = 21, 6 carcinoid tumors and 15 pancreatic NETs), other carcinoid tumors (n = 3), other NETs (n = 4), medullary thyroid carcinoma (MTC) (n = 1), and Merkel cell carcinoma (n = 1). Six patients had a syndrome related to endocrine hypersecretion. One hundred fifty-four therapy cycles were delivered (median, six per patient), and all patients could be evaluated for response on the basis of intent-to-treat analysis.

RESULTS. There were 9 objective responses: 2 complete responses (in 1 patient with Merkel cell carcinoma and 1 with pancreatic NET) and 7 partial responses (in 3 patients with pancreatic NETs, 2 with other NETs, 1 with GEP carcinoid tumor, and 1 with MTC). The median duration of response was 10 months (range, 5+ to 24+ months). No reduction in symptoms was achieved among the six patients with endocrine hypersecretion syndrome. Levels of urinary 5-hydroxyindoleacetic acid and serum chromogranin A were decreased in 50% and 14% of patients, respectively, who presented with abnormal baseline values. Treatment toxicity was acceptable and included nausea and vomiting, alopecia, leukopenia, and mucositis.

CONCLUSIONS. This trial demonstrated that the FDE regimen may be at least as effective as other systemic regimens. Comparison of this experience with the authors' previous trial revealed a noteworthy increase in the activity of the intensified regimen, especially in GEP NETs (the most chemoresistant tumors). Continued clinical research to improve these results is highly justified. ***Cancer* 1998;83: 372–8.** © *1998 American Cancer Society.*

KEYWORDS: carcinoid, neuroendocrine tumors, islet cell carcinoma, chemotherapy, chromogranin A.

Neuroendocrine tumors (NETs) include a wide variety of malignancies arising from the diffuse neuroendocrine system.[1,2] The most frequently encountered NETs (carcinoid tumors, islet cell tumors, or pancreatic NETs) originate from the gastroenteropancreatic (GEP) tract, but this group of neoplasms also includes medullary thyroid

carcinoma, Merkel cell carcinoma, and all tumors with neuroendocrine biologic characterization. Small cell lung carcinoma is excluded from this group because of its different clinical behavior.[1]

Occurrences of NETs inside solid tumors are rare. They are characterized by a low proliferation rate (particularly evident in GEP tumors), symptoms related to endocrine hypersecretion, the presence of specific circulating biologic markers, and the expression of somatostatin receptors. However, there is no other group of human neoplasms whose natural history can vary so greatly.

Tumor biology researchers are currently developing diagnostic procedures and new therapeutic strategies; however, despite the acquisition of important information and the development of highly potent pharmacologic drugs, the therapeutic approach must always include the possibility of surgery, which should be considered (if only for the purpose of debulking) even in the metastatic phase.[3]

The introduction into clinical practice of somatostatin analogs and interferons has significantly improved our therapeutic arsenal because of their high degree of effectiveness in controlling clinical manifestations related to hormone overproduction, such as carcinoid syndrome. Unfortunately, the antiproliferative effects of these drugs are disappointing, and the overall response rate is generally less than 10%.[3–6]

There is disagreement concerning the usefulness of chemotherapy in treating patients with these tumors. Streptozotocin (STZ) and chlorozotocin have been found to have therapeutic activity in islet cell carcinoma, but their severe toxicity compromises patients' quality of life;[7] moreover, our own experience with the association of STZ and epirubicin (EPI) was disappointing.[8] The use of dacarbazine (DTIC), anthracyclines, and 5-fluorouracil (5-FU) as single agents has generated response rates of up to 25%.[3] Polychemotherapy may improve these results.[9] In a previous study, we treated 38 NET patients with a combination of 5-FU, DTIC, and EPI (the FDE regimen); this treatment was very well tolerated, but the objective response rate was suboptimal.[10] We consequently decided to evaluate whether dose intensification could lead to better results, and we tested an intensified FDE regimen to evaluate its efficacy and tolerability in a group of patients with progressive, advanced NETs.

PATIENTS AND METHODS

Eligibility

All patients were required to have histologically proven locally advanced or metastatic NETs that were not amenable to surgery, with bidimensionally measurable lesions documented by chest X-ray, computed tomography (CT), or a physical examination. The patients could have been previously treated by means of surgery or with somatostatin analogs and/or interferons, but not with systemic chemotherapy. Patients were excluded if they had abnormal renal or hepatic function (serum bilirubin levels 2.5 mg/dL, liver enzyme aspartate aminotransferase and/or alanine aminotransferase 2.5 times the normal institutional level, or serum creatinine concentrations 1.5 mg/100mL), relevant myelodepression (white blood cell count $<4000/mm^3$ and/or platelet count ^{3}), or severe concomitant illness. All patients had to give written informed consent, and the treatment program was approved by the Human Investigation Committee of the Istituto Nazionale Tumori in Milan.

Pretreatment Evaluation and Response Assessment

The pretreatment evaluation consisted of history and physical examination, complete biochemical profile, and instrumental tests (CT scans, chest X-ray, abdominal ultrasound, and octreoscan); levels of serum neuron specific enolase (NSE), chromogranin A (CgA), and 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) were followed as available. Serum NSE was evaluated by means of an immunoradiometric assay kit supplied by AB Sangtec Medical (Bromma, Sweden); plasma CgA was measured using an enzyme-linked immunosorbent assay kit purchased from DAKO A/S (Glostrup, Denmark); 24-hour urine 5-HIAA was evaluated using a radioimmunoassay kit supplied by DDV Diagnostika (Marburg, Germany). A complete tumor response assessment was performed every three chemotherapy cycles.

Treatment

The treatment regimen involved the administration on 3 consecutive days of FU 500 mg/m^2 i.v. as a daily bolus, DTIC 200 mg/m^2 i.v. over 30 minutes, and EPI 30 mg/m^2 i.v. as a daily bolus. Adequate i.v. hydration and antiemetics were administered. The cycles were repeated every 3 weeks if absolute neutrophil counts were $\geq 1{,}500/mm^3$ and platelet counts were $\geq 100{,}000/mm^3$; treatment was delayed by 1 week if patients had inadequate bone marrow recovery at the time a new cycle was due. In cases of persistent myelotoxicity, chemotherapy was delayed further and the dose reduced by 25%. Responding patients received a maximum of nine courses.

Response and Toxicity Criteria

Treatment efficacy was evaluated in terms of objective response (tumor growth control), biochemical response (the control of biochemical markers), and

symptomatic response (the control of symptoms related to endocrine hypersecretion). Objective responses were defined according to World Health Organization criteria.[11] A complete response (CR) was defined as the complete disappearance of all evident tumor, as determined by 2 observations no less than 4 weeks apart; partial response (PR) was defined as a decrease of more than 50% in the cross-sectional area of the measurable lesions, as determined by 2 observations no less than 4 weeks apart; stable disease (SD) was defined as a change of less than 25% in the extent of the disease, with no appearance of new lesions; and progressive disease (PD) was defined as an increase of more than 25% in the area of measurable disease, or the appearance of new lesions. Biochemical response was defined as the return of high tumor marker levels to within the normal range or a shared decrease of 50% or more in comparison with baseline values. Symptomatic response was defined as the resolution of presenting symptoms or a reduction of 50% or more.

Survival and the time to treatment failure were measured as the interval between the date of patient registration and the date of disease progression or death. The duration of objective CR or PR was calculated from the date of a documented response to the date on which PD was first recorded; the duration of SD was defined as the time between the date of registration and the date on which PD was first observed. Side effects were evaluated at the beginning of each cycle and graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).[12]

RESULTS

Patient and Tumor Characteristics

Between March 1995 and January 1997, 30 consecutive patients were observed at the Division of Medical Oncology B of the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan; their characteristics are summarized in Table 1. There was an even balance of males and females, their median age was 55 (range, 19–72) years, and most had a good performance status. Carcinoid and pancreatic NETs were the most frequent. Six patients had a syndrome related to endocrine hypersecretion. All of the eligibility criteria were satisfied.

The primary sites of the carcinoid tumors were the GEP tract in six cases and the bronchi in three. The primary tumor was still present in 17 patients, had been previously excised in 11, and remained undetected in 2. Twenty patients had multiple disease sites. The most common disease sites were the liver (22 patients, 73%), followed by the pancreas (12), lymph nodes (10), peritoneum (4), spleen (3), and lung (3).

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Total	30
Male/female	15/15
Performance status 0–1/2 (ECOG scale)	26/4
Median age, yrs (range)	55 (19–72)
Histologic type	
Carcinoid	9
Gastroenteropancreatic	6
Lung	3
Pancreatic neuroendocrine tumors	15
Merkel cell carcinoma	1
Medullary thyroid carcinoma	1
Other NETs	4
Markers (biochemical abnormalities/patients evaluated)	
5-hydroxyindoleacetic acid	4/19
Chromogranin A	21/27
Neuron specific enolase	11/24
Prior treatment	
Surgery	11
Somatostatin analogs	5
Radiation therapy	3
Hepatic chemoembolization	2
Symptoms of endocrine hyperfunction	
Diarrhea	1
Diarrhea and flushing	2
Other	3

ECOG: Eastern Cooperative Oncology Group; NETs: neuroendocrine tumors.

Previous treatments included surgery for 11 patients, endocrine therapy for 5, radiation therapy for 3, and chemoembolization of hepatic metastases for 2; 15 patients had not received any previous therapy. In the patients with syndrome, the presenting manifestations were diarrhea in one case, diarrhea and flushing in two, increased serum adrenocorticotropic hormone level in one, and glycemic abnormalities in two. Elevated serum NSE values were detected in 11 (46%) of the 24 patients who could be evaluated biochemically, and abnormal CgA levels were detected in 21 of 27 (78%). Increased 5-HIAA urinary excretion was present in 4 of the 19 patients who could be evaluated (21%). Scanning with ^{111}In-radiolabeled pentreotide (octreoscan) confirmed disease extension in 16 of the 18 patients who underwent the procedure.

One hundred fifty-four therapy cycles were administered, with a median of 6 courses for each patient (range, 1–9): 141 courses were delivered at full dose, 8 at 75% of the programmed dose, and 5 at 66%. The reductions were due to treatment-related toxicity, including hypersensitivity, thrombocytopenia, abnormal hepatic function, a low performance status, and mucositis. The reduction of the dose at 66%, i.e., 2 days of chemotherapy instead of 3 days each cycle,

TABLE 2
Objective Responses to Treatment

	No. (%) of patients			
Intent-to-treat analysis	All tumors	GEP carcinoid tumors	Pancreatic NETs	Others
Eligible patients	30	6	15	9
Response to treatment				
CR	2 (7%)	—	1 (7%)	1 (11%)
PR	7 (23%)	1 (17%)	3 (20%)	3 (33%)
CR+PR	9 (30%)	1 (17%)	4 (27%)	4 (44%)
SD (>6 mos)	10 (33%)	2 (33%)	5 (33%)	3 (33%)
TF	11 (37%)	3 (50%)	6 (40%)	2 (22%)

GEP: gastroenteropancreatic; NET: neuroendocrine tumor; CR: complete response; PR: partial response; SD: stable disease; TF: treatment failure.

was employed in 2 patients who presented, after the first cycle, with hepatotoxicity and mucositis, respectively, although this kind of reduction was not defined in the protocol. Ten patients (33%) received the treatment without any dose reduction or delay. Twenty-one cycles were administered without DTIC (5-FU and EPI only) because that drug was unavailable for pharmaceutical company reasons between October 1996 and January 1997. All of the chemotherapy cycles were administered in an outpatient setting.

Response

All of the patients were assessable for objective response on the basis of intent-to-treat analysis. There were two complete responders (one with a pancreatic NET and one with a Merkel cell carcinoma) and seven partial responders (three patients with pancreatic NETs, two with other NETs, one with a GEP carcinoid tumor, and one with MTC) (Table 2). The median time to response was 2 (range, 1–5) months. After a median follow-up of 13 (range, 5–28) months, the median duration of response was 10 (range, 5+ to 24+) months. Given the slow tumor growth and the short follow-up, median overall survival has not yet been reached. We achieved an overall response rate of 30% (exact 95% confidence interval, 14.7–49.4%). In relation to the tumors of GEP origin (carcinoid tumors and pancreatic NETs), which were characterized by slow growth and poor responsiveness to chemotherapy, a noteworthy 24% overall response rate was achieved. The patients with other histotypes that were potentially more responsive to chemotherapy had an overall response rate of 44%. The characteristics of the responding patients are listed in Table 3. Disease stabilization for at least 6 months was documented by means of radiologic examinations in 10 patients.

At the end of treatment, six of the responding patients underwent surgery: a complete pathologic response was documented in two cases, three patients underwent radical surgery, and one underwent debulking.

No symptomatic responses were observed in the six patients with syndrome. Three of the 11 patients with increased serum NSE levels showed a documented reduction with respect to baseline (2 CR and 1 PR, an overall response rate of 27%). A decrease in serum CgA levels was observed in 3 of 21 patients (1 CR and 2 PR, an overall response rate of 14%). One carcinoid patient showed a biochemical CR in terms of 5-HIAA and one a PR (overall response rate, 50%).

Toxicity

Of the 30 treated patients, 26 could be evaluated for toxicity. With regard to the other four patients, two continued therapy in other hospitals, for whom we have no information about side effects; one was lost to follow-up after the first cycle; and one died after the first cycle due to early disease progression. The treatment regimen was well tolerated (Table 4), the most common side effects being nausea/vomiting and mucositis. Only 2 patients experienced Grade 3 stomatitis. Alopecia was universal. The other recorded side effects were asthenia (eight patients), infection (six patients), diarrhea (three patients), and cutaneous rash (one patient). In terms of hematologic toxicity, Grade 1–2 neutropenia was documented in 4 patients and Grade 3 in 7. Seven patients experienced Grade 1–2 anemia and two Grade 3; one patient experienced Grade 1 thrombocytopenia. Fourteen patients (47%) required a treatment delay due to myelotoxicity; 38 courses (25%) were delayed for 7 days or less, whereas 6 (4%) were delayed by more than 7 days.

DISCUSSION

Therapeutic choices for patients with advanced NETs are greatly influenced by tumor distribution and burden, disease aggressiveness, and the nature and severity of the associated endocrine syndromes. Surgery must always be considered, as it is the only approach that may improve patient survival; however, hepatic chemoembolization, systemic chemotherapy, and specific drugs for the suppression of hormone production (e.g., octreotide for carcinoids and omeprazole for gastrinoma) should also be taken into account.[3] Because of the extremely heterogeneous nature of these neoplasms, the current tendency is to personalize the treatment for each patient, using the various available therapies in turn.

The standard chemotherapy options for the management of NETs and the time at which cytotoxic therapy should be given remain undetermined. 5-FU,

TABLE 3
Characteristics of Responding Patients

Age (yrs)/PS/ Gender	Histologic type	Octreoscan	Symptomatic response	Prior therapy	Sites of disease	Objective response	Biochemical response	Time to response (mos)	Response duration (mos)
54/2/F	Merkel cell carcinoma	ND	No syndrome	—	Pelvic mass	CR	—	2	21+
66/0/M	Pancreatic NET	ND	No syndrome	—	Pancreas, liver	PR	CgA PR NSE PR	2	10
56/0/F	Other NET	Positive	No syndrome	Surgery	Liver	PR	NSE NC 5HIAA NC	1	16
55/0/F	Pancreatic NET	ND	No syndrome	—	Pancreas, lymph nodes	CR	—	2	24+
49/0/M	Pancreatic NET	Positive	NC	SMS analogs	Pancreas, spleen	PR	NSE CR	1	9
27/1/M	Other	Negative	No syndrome	Surgery	Liver, bone, lymph nodes, lung, adrenal gland	PR	CgA NC	1.5	10+
	NET						NSE NC		
42/0/M	Pancreatic	Positive	NE	—	Pancreas, liver, lymph nodes, spleen	PR	CgA CR	4	7+
	NET						NSE NC 5HIAA NC		
64/0/M	GEP	Positive	No syndrome	Surgery	Lymph nodes, peritoneum	PR	CgA NC	4	6+
	carcinoid tumor						NSE NC		
38/0/F	MTC	Negative	No syndrome	Surgery, radiation therapy	Lung, lymph nodes	PR	—	5	5+

PS: performance status; NET: neuroendocrine tumor; GEP: gastroenteropancreatic; MTC: medullary thyroid carcinoma; ND: not done; NC: no change; NE: could not be evaluated; SMS: somatostatin; CR: complete response; PR: partial response; CgA: chromogranin A; NSE: neuro specific enolase; 5-HIAA: 5-hydroxyindoleacetic acid.

TABLE 4
Incidence of Side Effects (Among 26 Patients Evaluated)

	NCI-CTC Grade		
	1–2	3	Total
Side effect	No. (%) of patients		
Neutropenia	4	7	11 (42%)
Anemia	7	2	9 (35%)
Thrombocytopenia	1	—	1 (4%)
Nausea/vomiting	18	—	18 (69%)
Stomatitis	12	2	14 (54%)
Asthenia	8	—	8 (31%)
Infection	6	—	6 (23%)
Diarrhea	3	—	3 (12%)
Rash	—	1	1 (4%)
Alopecia	—	26	26 (100%)
Other	10	—	10 (38%)

NCI-CTC: National Cancer Institute-Common Toxicity Criteria.

which is used in various schedules, is considered to be one of the most effective drugs for advanced carcinoid tumors, with an objective response rate of up to 26%.[13] Its association with other drugs (e.g., STZ, doxorubicin and interferons) only moderately improves its activity.[14–17] STZ seems to have a specificity for advanced islet cell carcinoma, and its combination with 5-FU or doxorubicin enhances its therapeutic efficacy in terms of tumor regression and the control of endocrine syndromes.[7] However, these noteworthy results cannot be achieved in other NETs, and the drug often produces severe toxicity (renal failure and nausea/vomiting); in any case, it is not available in Italy.

The combination of cisplatin and etoposide has a documented high degree of activity (ORR, 67%; median survival, 19 months) in anaplastic neuroendocrine carcinoma, similar to that obtained in extensive small cell lung carcinoma; however, its activity in 27 patients with well-differentiated neoplasms in the same study was poor (ORR, 7%).[18]

Somatostatin (SMS) analogs have been demonstrated to produce a biologic response in the majority of patients with carcinoid syndrome; however, objective tumor regressions occur only sporadically. On the other hand, some data and a previous study of our

group (I.T.M.O.)[4] suggest that octreotide may lead to long term disease stabilization and that it may offer a survival advantage to patients with carcinoid syndrome.[6,19]

Interferons also appear to be active in this group of neoplasms: Eriksson et al. have documented an interesting 33% ORR with a median duration of 17+ months using nonrecombinant human leukocyte interferon to treat patients with islet cell tumors,[20] but few other studies have confirmed these promising results.[5]

The objective of the current trial was to determine the efficacy of the combination of 5-FU, DTIC, and EPI as a treatment for patients with advanced NETs. Our previous experience with a similar regimen was disappointing: we demonstrated its good tolerability, but its antitumor activity was quite modest, at least in GEP tumors (ORR, 10%; median duration, 5 months).[10] However, given the low incidence of side effects, we had the impression that the results may have been influenced by an inadequate dose intensity, so we decided to evaluate an intensified regimen.

The treatment schedule included 5-FU at a dose of 500 mg/m^2, EPI at 30 mg/m^2, and DITC at 200 mg/m^2; in the previous study, the doses were 250 mg/m^2 (5-FU), 25 mg/m^2 (EPI), and the same for DTIC. This dose intensification did allow a moderate improvement in the results obtained with the original schedule. It is worth noting that six of nine responding patients, all of whom had been unsuitable for surgery before treatment, underwent surgery. We think that this is the chemotherapeutic goal, particularly regarding GEP tumors, for which debulking procedures make it possible to achieve a survival advantage as well as a symptomatic benefit.[21] However, the overall response rate observed with GEP tumors (24%, with a median duration of 9 months) cannot be considered adequate, and once again the low degree of chemoresponsiveness of these neoplasms is underscored. It is not possible to give an overall evaluation of the efficacy of the regimen in treating the other NETs because of their heterogeneity. The complete pathologic response for 21+ months obtained in the patient with Merkel cell carcinoma confirms the high degree of chemoresponsiveness of this histologic type; it is worth noting that this patient had a bulky pelvic mass at the beginning of treatment. A noteworthy result was also achieved in the MTC patient, whose PRs in the lung and lymph nodes lasted 5+ months.

Finally, it is important to point out that only one of the responding patients received more than one chemotherapy cycle without DTIC, which may indicate the importance of DTIC to this regimen.

Our data confirm that NETs represent a wide group of neoplasms with different degrees of chemoresponsiveness.

Immunohistochemistry and other techniques for recognizing neuroendocrine features are now available, thus making it possible to distinguish what were previously considered undifferentiated adenocarcinomas. It is possible that NETs may be more common than once believed.[22] There is one group of NETs that seems to have a less well developed neuroendocrine pattern, greater cytologic atypia, and higher mitotic activity than carcinoid and islet cell carcinoma; this "aggressive" group, which is less frequently associated with hormone overproduction, is more chemosensitive than the classical GEP tumors.

This study demonstrated that the combination of 5-FU, DTIC, and EPI may be at least as effective as other systemic regimens for the palliation of rapidly progressive metastatic NETs. It also demonstrated the feasibility of this regimen and confirmed the poor efficacy of chemotherapy in alleviating the symptoms related to endocrine hypersecretion, such as diarrhea and flushing. Preclinical studies have demonstrated that octreotide may enhance the antimitotic activity of 5-FU and doxorubicin.[23] In future studies, perhaps the combination of chemotherapy and SMS analogs (possibly in the new, long-lasting formulations) should be used in an attempt to increase the number of objective responses as well as offer better syndrome control.

A comparison of this study with our previous trial, in which similar polychemotherapy was used, revealed a noteworthy increase in the activity of the intensified regimen, especially in GEP tumors (the most chemoresistant group). However, the results are still not satisfactory, and so there is an urgent need to find new therapeutic approaches that are truly effective against this category of tumors and strong justification for continuing clinical research in this area.

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