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ORIGINAL REPORT

Fluorouracil, Doxorubicin, and Streptozocin in the Treatment of Patients With Locally Advanced and Metastatic Pancreatic Endocrine Carcinomas

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
The role of systemic chemotherapy in the management of pancreatic endocrine carcinoma (islet cell carcinoma; PEC) is an area of considerable controversy. Response rates ranging from 6% to 69% have been reported for streptozocin-based chemotherapy. We retrospectively studied 84 patients with locally advanced or metastatic PEC who had been treated with fluorouracil, doxorubicin, and streptozocin (FAS) to determine the objective response rate, duration of progression-free survival (PFS), and duration of overall survival (OS).

Patients and Methods
Eligible patients had histologic or cytologic confirmation of their tumor and measurable disease on computed tomography or magnetic resonance imaging scans. Response to treatment was evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee.

Results
Sixty-one of the patients were male and 23 were female, with a median age of 54 years (range, 24 to 78 years). The response rate (RR) to FAS was 39%, with a median response duration of 9.3 months. The 2-year PFS rate was 41%, and the 2-year OS rate was 74%. The extent of liver metastatic disease correlated with a worse PFS ($P = .01$ by log-rank test) and a worse OS ($P < .0001$ by log-rank test). Analyses showed that metastatic replacement of more than 75% of the liver and prior chemotherapy were independently associated with inferior PFS.

Conclusion
Patients with locally advanced or metastatic PEC who are treated with FAS may have a reasonable RR, and responders may experience longer PFS and OS. The volume of metastases in the liver is the most important predictor of outcome.

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INTRODUCTION

Pancreatic endocrine carcinomas (PECs), also known as islet cell carcinomas, are rare neoplasms of neuroectodermal origin.[1] Most are sporadic; however, they may also develop in the setting of multiple endocrine neoplasia type I, von Hippel-Lindau disease, neurofibromatosis 1, and tuberous sclerosis.[2] Multiple hormones and peptides are frequently produced by PECs. Functioning PECs release biologically active substances, or hormones, that produce distinct clinical syndromes. These hormones include gastrin, insulin, glucagon, somatostatin, vasoactive intestinal polypeptide, growth hormone–releasing factor, and adrenocorticotropic hormone. Nonfunctioning PEC may also secrete a number of amines and peptides (eg, neurotensin, the α-subunit of human chorionic gonadotropin, neuron-specific enolase, pancreatic

polypeptide, and chromogranin A); however, these are inactive and do not produce recognizable clinical syndromes. Because of their indolent nature, the diagnosis is often delayed (4 to 6 years) and PECs become clinically apparent when they already are inoperable or metastatic.[2]

Despite their indolent course, PECs can be aggressive and resistant to therapy. Complete surgical resection is the treatment of choice for localized cancers. However, PECs frequently are unresectable because of distant metastatic disease or local extension of the tumor. Because of the heterogeneity, the varying degree of aggressiveness, and the lack of a standard approach to their management, these cancers offer a special challenge.[3] The therapeutic options include cytoreductive surgery, biotherapy with interferon alfa, suppression of hormonal production with somatostatin analogs, hepatic artery embolization or chemoembolization, and systemic chemotherapy. Somatostatin analogs are effective in controlling hormone-related symptoms.[4] Treatment with interferon alfa may result in a biochemical response, in which fewer patients realize reduction in tumor volume. Embolization and chemoembolization, which may decrease tumor bulk and help control the symptoms associated with excessive hormones, are generally reserved for patients with metastatic tumors that failed to respond to other treatments.

Systemic chemotherapy has been evaluated, with variable rates of tumor response. Single chemotherapeutic agents used include streptozocin, fluorouracil (FU), doxorubicin, chlorozotocin, and dacarbazine, but usually produce low response rates (RRs). Combinations of streptozocin-based chemotherapy may produce a higher RR. The combination of streptozocin with doxorubicin is a frequently used first-line regimen based on the Eastern Cooperative Oncology Group randomized trial.[5-8] However, more recent studies, reporting response rates as low as 6%, have failed to confirm these results.[9,10] Previous studies have used the triple chemotherapy of FU, doxorubicin, and streptozocin (FAS) and shown promising RR, although the number of patients analyzed was small.[7,8] Therefore, the role of systemic chemotherapy in advanced PEC remains to be determined.

In this study, we retrospectively examined the objective tumor RR, duration of progression-free survival (PFS), and duration of overall survival (OS) in 84 patients with locally advanced or metastatic PEC treated with combination FAS chemotherapy.

PATIENTS AND METHODS

Patients

Approval for data collection and analyses was obtained from The University of Texas M.D. Anderson Cancer Center (Houston, TX) institutional review board. The study group included 84 consecutive patients with locally advanced and metastatic PEC who received FAS at The University of Texas M.D. Anderson Cancer Center between January 1992 and September 2003. To be eligible, patients also had to have histologic or cytologic confirmation of their tumor and measurable disease on computed tomography (CT) or magnetic resonance imaging (MRI) scans. Serum levels of chromogranin A were measured before (n = 60) and within 4 months (n = 49) of the first cycle of chemotherapy. The amount of liver metastasis was classified as less than 50%, 50% to 75%, and more than 75%.

Chemotherapy

The regimen included an intravenous 400 mg/m^2 bolus of FU daily on days 1 to 5; a 400 mg/m^2 bolus of streptozocin daily on days 1 to 5, and a 40 mg/m^2 bolus of doxorubicin on day 1. Cycles were repeated every 28 days. The median number of chemotherapy cycles was four (range, one to 16) and the median duration of treatment was 3.9 months (range, 5 days to 15.5 months). Full blood counts including absolute neutrophil counts and platelets, as well as biochemical studies, were obtained before the first course and every course thereafter in all patients. Doses were reduced at the beginning of the treatment in patients with hyperbilirubinemia or uncontrolled diabetes. Reduction of streptozocin dose to 300 mg/m^2 was adjusted for patients with uncontrolled diabetes because streptozocin may damage normal pancreatic cells. Doses were also adjusted at the start of a subsequent course if grade 3 or 4 toxicity was observed. Occasionally, grade 1 to 2 toxicities led to dose reduction or to delay of the treatment. All patients were re-evaluated every 8 weeks after the initiation of treatment to assess their clinical status and their response to therapy. The evaluation comprised a complete physical examination and tumor measurement by CT or MRI. Fasting tumor markers, bone scan, and somatostatin receptor scintigraphy were obtained as needed. Chemotherapy was continued until disease progression, unacceptable toxicity, or patient intolerance. Cardiac function was evaluated in all patients after the sixth or seventh course of chemotherapy by echocardiogram. Doxorubicin was reduced or discontinued when the left ventricular ejection fraction was reduced more than 10% to 15% of the initial value, or if it was below the lower normal limit.

Evaluation of Tumor Response

All CT or MRI reports were available, and the original films were also re-evaluated independently by two physicians (M.A.K. and J.C.Y.). Patients were considered assessable only if measurable disease was present. Response to treatment was evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[11]; complete response (CR) was defined as the disappearance of all lesions. Partial response (PR) was defined as at least a 30% reduction in the tumor load, estimated as the sum of the longest diameters (LD) of all measurable lesions, taking as a reference the baseline sum of LD. Progressive disease (PD) was defined as at least a 20% increase in the tumor load, taking as a reference the smallest sum of LD recorded since the treatment started or development of new lesions in a previously uninvolved site. Stable disease (SD) was defined as disease that showed neither sufficient shrinkage nor increase to qualify as either PR or PD.

Duration of overall response was defined as the time between the initial documented response and the first date of recurrence or progression. Duration of SD was defined as the time between the date treatment started and the first date of recurrence or progression.

Statistical Analysis

The comparisons between response and tumor characteristics, disease extension, or laboratory features were based on χ^2 and Fisher's exact tests, as appropriate. PFS was measured from the beginning of treatment to progression, relapse, death, or last follow-up. OS was measured from the beginning of treatment to the time of last follow-up or death. Actuarial survival was measured by the method of Kaplan and Meier.[12] The statistical differences in PFS between groups of patients were estimated by the log-rank test.[13] The statistical independence between prognostic variables was evaluated by multivariate analysis using the Cox proportional hazards model.[14] All statistical calculations were performed using StatView (Abacus Concepts, Berkeley, CA). Differences were considered statistically significant when the *P* value was less than .05.

RESULTS

Response to Treatment

We identified 84 patients (61 males and 23 females) with locally advanced or metastatic PEC treated with FAS. The median age at the time of initiation of chemotherapy was 54 years (range, 24 to 78 years). The clinical characteristics of the patients are listed in Table 1. Sixty-four of the tumors were nonfunctioning, 11 were gastrinomas, three were insulinomas, three were glucagonomas, two were vasoactive intestinal polypeptide tumors, and one was an adrenocorticotropic hormone–producing PEC. All eight locally advanced tumors were nonfunctioning.

Eleven of 84 patients were previously treated with somatostatin analogs (n = 5), hepatic artery chemoembolization (n = 4), or both (n = 1); one additional patient underwent radiofrequency ablation of the liver. One patient continued receiving the somatostatin analogs during his treatment with FAS chemotherapy. In addition, three patients received somatostatin analogs along with FAS.

Of the entire group of 84 patients, 33 (39%; 95% CI, 27 to 50) responded to chemotherapy, 42 (50%) had SD, and disease progressed in nine (11%). Four patients were able to have curative resection of their tumors after PR. The median duration of response was 9.3 months (range, 2.3 to 51 months), and the median time to response was 3.9 months (0.7 to 14.2 months). None of the 11 patients with metastatic gastrinomas responded to chemotherapy, compared with 33 of 73 patients (45%) with all other tumor types (P = .002 by Fisher's exact test). Four of nine patients (44%) with functioning tumors other than gastrinomas responded to FAS. RRs by hormone production status are listed in Table 2. Figure 1 shows CT scans of three patients who responded dramatically to chemotherapy. Patients with locally advanced tumors did not differ from those with metastatic tumors in terms of RR. Similarly, the volume of liver disease was not statistically associated with different RR. The RR for the group of patients (n = 21) with extrahepatic distant metastases with or without liver involvement was 19% compared with 47% for the group of patients (n = 55) with liver metastases only (P = .03 by Fisher's exact test; Table 2). Previous treatment with other chemotherapy or other modalities did not affect RR.

Table 1. Characteristics of 84 Patients Included in the Study

Characteristic	No. of Patients
Sex	
Male	61
Female	23
Age at treatment, years	
Median	54
Range	24-78
Interval from diagnosis to treatment, months	
Median	2.6
Range	0.2-199
Tumor type	
Functioning	20
Gastrinoma	11
Insulinoma	3
Glucagonoma	3
VIPoma	2
ACTH-producing PEC	1
Nonfunctioning	64
Inheritance	
MEN1	4
Sporadic	80
Tumor status	
Locally advanced	8 (all nonfunctioning tumors)
Metastatic	76 (73 LM [18 plus ODM]/3 ODM)
% of liver replaced by metastases	
≤ 50/> 50	44/29
≤ 75/> 75	61/12
Treatment trial	
First line	79
Second line	5

Abbreviations: VIPoma, vasoactive intestinal polypeptide; ACTH, adrenocorticotropic hormone; PEC, pancreatic endocrine carcinoma; MEN1, multiple endocrine neoplasia type I; LM, liver metastases; ODM, other distant metastases.

Pretreatment measurements of serum chromogranin A were available for 60 patients. Forty-five of 54 metastatic tumors (83%) showed increased pretreatment levels of chromogranin A, compared with two of six locally advanced tumors (33%; P = .01 by Fisher's exact test). Chromogranin A measurements within 4 months of the initiation of chemotherapy were available for 49 patients. Response to chemotherapy was associated with a decrease in the pretreatment levels of serum chromogranin A of at least 30% (12 of 24 *v* six of 27; P = .04 by Fisher's exact test). Neither tumor type nor disease extension was significantly associated with the decrease in serum chromogranin A levels after chemotherapy.

Thirty-seven patients who experienced disease progression during or after the treatment, as well as four

Table 2. Response to Chemotherapy

Parameter	Response Rate			Stable Disease		Progressive Disease	
	No. of Patients	%	P*	No. of Patients	%	No. of Patients	%
All patients	33	39	NA	42	50	9	11
Tumor status			NS				
Locally advanced	2	25		6	75	0	
Metastatic	31	41		36	47	9	12
LM			NS				
≤ 75%	27	44		26	43	8	13
> 75%	4	34		7	58	1	8
Sites of metastases			.02				
Liver only	27	49		22	40	6	11
Liver ± other sites	4	19		14	67	3	14
Tumor type			.002				
Gastrinomas	0			9	8	2	18
All other PEC	33	45		33	45	7	10
Decrease of chromogranin A after treatment			.04				
≥ 30%	12	67		6	33	0	
< 30%	12	36		16	49	5	15

Abbreviations: NA, not applicable; NS, not significant; LM, liver metastases; PEC, pancreatic endocrine carcinoma.
*By Fisher's exact test.

patients with SD, were subsequently treated using other modalities including second-line chemotherapy, hepatic artery chemoembolization, somatostatin analogs, or interferon.

Dose Intensity and Toxic Reactions

Of the entire group of 84 patients, seven patients received a reduced first dose of FAS because of diabetes and mild renal insufficiency (n = 2), jaundice (n = 2), poor performance status (n = 2), and previous external-beam radiation therapy to the pelvis for colon carcinoma (n = 1). In subsequent chemotherapy courses (after the first course), eight patients needed dose reduction: three because of grade 3 or 4 toxicity and five because of recurrent grade 1 or 2 toxicity. Delay in administration of the treatment occurred on 13 occasions because of grade 3 or 4 toxicity (n = 7), or grade 1 or 2 toxicity (n = 4). Two additional patients had delays in the scheduled chemotherapy dates because they underwent surgery for reasons unrelated to their disease. In eight patients, at least one of three drugs was withheld because of toxic reactions or poor tolerance. In addition, doxorubicin was discontinued in five patients because they had received the maximum accumulated lifetime dose.

The grade 3 or 4 toxic reactions to FAS are listed in Table 3. In total, grade 3 or 4 toxic reactions occurred in 19 of 84 patients (23%). The most common toxic reactions attributable to the whole treatment included nausea, vomiting, myelosuppression, and fatigue. In addition, alopecia was almost invariably observed. Mild nausea and vomiting occurred in most patients, usually within the 5 days of the treatment. Mild to moderate diarrhea (fewer than seven episodes per day) and mild mucositis also developed in some patients. One patient developed intolerable vomiting and diarrhea intractable to treatment and required hospitalization for dehydration. Eleven patients developed grade 3 or 4 neutropenia (absolute neutrophil counts, $< 1.0 \times 10^9$/L), and three of them were admitted to the hospital for neutropenic fever. In addition, one of these three patients had grade 4 thrombocytopenia (platelets, 19×10^9/L). None of the patients developed heart failure, although two had borderline left ventricular ejection fractions. In addition, two patients experienced acute myocardial infraction; one after the first and the other after the third course of treatment, and thus chemotherapy was withheld for them thereafter. One patient developed pulmonary embolism after the first treatment and was admitted to the hospital, and as a result there was a delay in the administration of the subsequent courses.

Clinical Outcome

In the entire study group of 84 patients, the median PFS was 18 months. At 2 years, PFS was 41% (95% CI, 26 to 56; Fig 2). After a median follow-up of 14 months (range, 2 to 62 months) for survivors, 39 of the patients (46%) treated with FAS had PD or experienced relapse after an initial CR or PR.

Median OS was 37 months. At 2 years, OS was 74% (95% CI, 61 to 87; Fig 2). Fifty-nine patients (70.5%) were alive; five patients were alive with no evidence of disease (one because of a CR to chemotherapy and the other four because of curative resection of the primary tumor, metastases, or both), 54 patients were alive with disease, and 25 patients were dead as a result of disease.

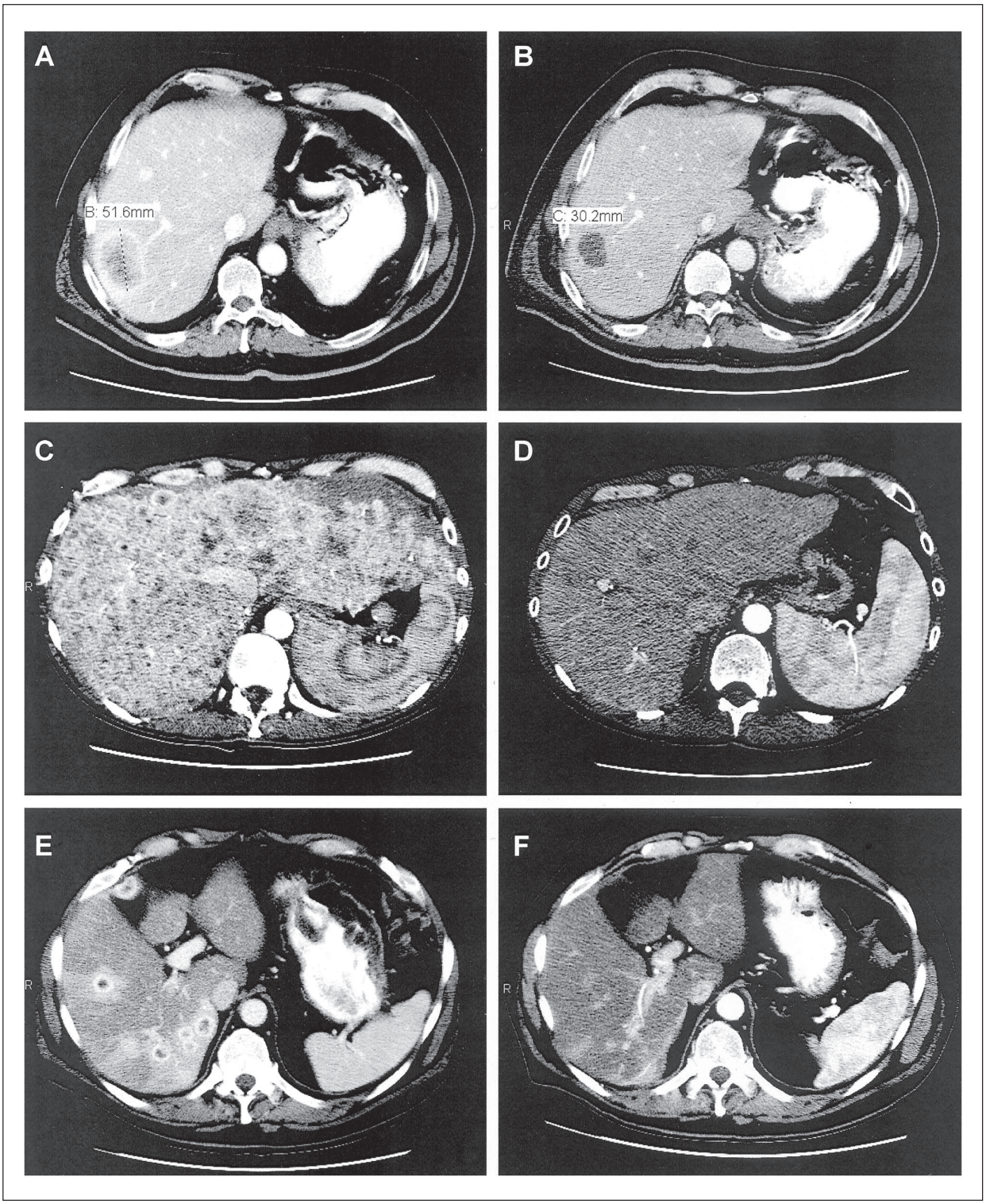

Fig 1. Patients with liver metastases who responded dramatically to chemotherapy. Patient 1, with (A) single hepatic metastasis, had (B) partial response (PR) after two cycles of fluorouracil, doxorubicin, and streptozocin (FAS). Patient 2, with (C) more than 75% metastatic replacement of the liver, showed (D) PR after four cycles of FAS. Patient 3, with (E) multiple metastatic sites on the liver, experienced (F) complete response after four cycles of FAS.

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