STREPTOZOCIN–DOXORUBICIN, STREPTOZOCIN–FLUOROURACIL, OR CHLOROZOTOCIN IN THE TREATMENT OF ADVANCED ISLET-CELL CARCINOMA

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Abstract *Background.* The combination of streptozocin and fluorouracil has become the standard therapy for advanced islet-cell carcinoma. However, doxorubicin has also been shown to be active against this type of tumor, as has chlorozotocin, a drug that is structurally similar to streptozocin but less frequently causes vomiting.

Methods. In this multicenter trial, we randomly assigned 105 patients with advanced islet-cell carcinoma to receive one of three treatment regimens: streptozocin plus fluorouracil, streptozocin plus doxorubicin, or chlorozotocin alone. The 31 patients in whom the disease did not respond to treatment were crossed over to chlorozotocin alone or to one of the combination regimens.

Results. Streptozocin plus doxorubicin was superior to streptozocin plus fluorouracil in terms of the rate of tumor regression, measured objectively (69 percent vs. 45 percent, P = 0.05), and the length of time to tumor progression (median, 20 vs. 6.9 months; P = 0.001). Streptozocin plus doxorubicin also had a significant advantage in terms of survival (median, 2.2 vs. 1.4 years; P = 0.004) that was accentuated when we considered long-term survival (>2 years). Chlorozotocin alone produced a 30 percent regression rate, with the length of time to tumor progression and the survival time equivalent to those observed with streptozocin plus fluorouracil. Crossover therapy after the failure of either chlorozotocin alone or one of the combination regimens produced an overall response rate of only 17 percent, and the responses were transient. Toxic reactions to all regimens included vomiting, which was least severe with chlorozotocin; hematologic depression; and, with long-term therapy, renal insufficiency.

Conclusions. The combination of streptozocin and doxorubicin is superior to the current standard regimen of streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. Chlorozotocin alone is similar in efficacy to streptozocin plus fluorouracil, but it produces fewer gastrointestinal side effects than the regimens containing streptozocin. It therefore merits study as a constituent of combination drug regimens. (N Engl J Med 1992; 326:519-23.)

ADVANCED carcinoma of the islet cells of the pancreas, although rare, presents a kaleidoscope of clinical challenges. In addition to the usual problems associated with primary and metastatic tumor bulk, patients with islet-cell carcinoma may have evidence of a variety of hormonal excesses — sometimes subclinical, sometimes life-threatening. A special feature of islet-cell carcinomas, which should be weighed in any treatment decision, is the frequently indolent progression of disease even after metastasis has occurred. Treatment options should always include judicious observation. The choice in cases of advanced disease is strongly influenced by the distribution and bulk of tumor, the aggressiveness of the disease, and the nature and severity of the associated endocrine syndromes. The appropriate treatment may include surgical reduction of tumor bulk, hepatic-artery occlusion for disease that is predominantly in the liver, specific end-organ blockade for endocrine syndromes (e.g., omeprazole for gastrinoma), suppression of hormone production (e.g., octreotide for the vasoactive intestinal peptide syndrome), and usually last in line, systemic cytotoxic therapy.

Streptozocin has been marketed specifically for the treatment of islet-cell carcinoma; it induces objectively measurable tumor regression in about one third of patients.[1] In an earlier study, our group found that a combination of fluorouracil with streptozocin produced a significant improvement in response rate and a trend toward improved survival when compared with the use of streptozocin alone.[2] We also found that doxorubicin was active in patients in whom previous chemotherapy had failed.[3] These findings led to the consideration of a combination of doxorubicin and streptozocin as therapy for this type of cancer. A pilot study found that these agents could be combined safely at essentially full doses of each (unpublished data). Chlorozotocin is a new drug that is structurally very similar to streptozocin; both contain a nitrosourea moiety. Its toxic effects include hematologic depression, but with less nausea and vomiting than are associated with streptozocin.[4,5] It also has the practical advantage of being administered in a single intravenous dose during each course of treatment.

The present study compared a combination of doxorubicin and streptozocin with the more commonly used combination of fluorouracil and streptozocin in metastatic islet-cell cancer. We also compared the new

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Performed for the Eastern Cooperative Oncology Group (D.C. Tormey, chair). Other participating institutions include Albany Medical College, Albany, N.Y.; Albert Einstein College of Medicine, Bronx, N.Y.; University of California–Irvine, Orange; Case Western Reserve University, Cleveland; Chicago Medical School, Chicago; Fox Chase Cancer Center, Philadelphia; Hahnemann Medical College, Philadelphia; Johns Hopkins Oncology Center, Baltimore; Medical College of Ohio, Toledo; University of Minnesota, Minneapolis; Mount Sinai Medical Center, New York; New York University Medical Center, New York; Newark Beth Israel Medical Center, Newark, N.J.; Northwestern University Medical Center, Chicago; Our Lady of Lourdes Hospital, Binghamton, N.Y.; Hospital of the University of Pennsylvania, Philadelphia; University of Pittsburgh, Pittsburgh; University of Rochester Cancer Center, Rochester, N.Y.; Roswell Park Memorial Institute, Buffalo, N.Y.; Rush–Presbyterian–St. Luke's Medical Center, Chicago; University of Pretoria, Pretoria, South Africa; the Swiss Group, Bern, Switzerland; Tufts–New England Medical Center Hospital, Boston; Natalie Warren Bryant Cancer Center, Tulsa, Okla.; and the University of Wisconsin Clinical Cancer Center, Madison.

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agent chlorozotocin with the two streptozocin combinations.

Methods

The patients enrolled in this trial were cared for at a number of different centers; the study was conducted by the Eastern Cooperative Oncology Group (ECOG). All those enrolled in the study had histologic proof of unresectable or metastatic islet-cell carcinoma. Tissue diagnosis was confirmed by pathological review. It was required that each patient have a measurable indicator of response to therapy, which could include evidence of tumor on physical examination or chest films or well-defined metastatic lesions in the liver on radioisotope or CT scanning, provided these lesions measured at least 5 cm at their widest point. Malignant hepatomegaly could be used as an indicator if there was a clearly palpable liver edge at least 5 cm below the xiphoid process or the costal margins during quiet respiration. For patients without measurable tumor, laboratory assays demonstrating excessive hormone production could be accepted as the only indicators of response. This was the case for only seven patients. The criteria for exclusion were an ECOG performance score of 4 (indicating total disability), severe nutritional impairment, recent major surgery (within three weeks), previous therapy with any of the study agents, any chemotherapy or radiation therapy within the previous month, active infection, a leukocyte count $<4\times10^9$ per liter or a platelet count $<150\times10^9$ per liter, active heart disease, a serum creatinine level >132.6 mmol per liter (1.5 mg per deciliter) or a blood urea nitrogen level >10.7 mmol per liter (30 mg per deciliter), or any elevation of serum bilirubin. Patients were also excluded if they had any other concurrent or recent malignant disease except cutaneous epitheliomas or cervical carcinoma in situ.

Randomization Procedures

Patients were stratified according to ECOG performance score and according to whether their indicator of response was measurable tumor or endocrine abnormalities on laboratory assays. They were then randomly assigned to therapy with chlorozotocin alone, fluorouracil plus streptozocin, or doxorubicin plus streptozocin. If the initially assigned treatment failed, the patients treated with chlorozotocin alone were randomly assigned to receive either fluorouracil plus streptozocin or doxorubicin plus streptozocin. Those originally assigned to a streptozocin regimen received chlorozotocin.

Treatment

Chlorozotocin was given in a single intravenous injection (150 mg per square meter of body-surface area), repeated every seven weeks. For the combination regimens, streptozocin was given by intravenous injection at a dose of 500 mg per square meter per day for five consecutive days, repeated every six weeks. Fluorouracil was given by intravenous injection at a dose of 400 mg per square meter per day for five days concurrently with streptozocin. Doxorubicin was given along with streptozocin by intravenous injection at a dose of 50 mg per square meter on days 1 and 22 of each six-week treatment cycle, with a maximal total dose of 500 mg per square meter. Leukocyte and platelet counts were obtained weekly; serum creatinine measurements and urinalyses were performed before each cycle of therapy. Dosages were reduced if patients had severe nausea or vomiting, stomatitis, diarrhea, leukopenia, or thrombocytopenia. If the creatinine level became elevated or persistent proteinuria developed, the dose of streptozocin or chlorozotocin was reduced. If these abnormalities persisted, treatment with these agents was discontinued. Therapy was continued until disease progression was noted.

Evaluation of Response

Patients treated with the drug combinations were reevaluated every six weeks, and those treated with chlorozotocin were reevaluated every seven weeks. Measurable tumor masses were considered to have regressed if the product of perpendicular diameters was reduced by at least 50 percent. For malignant hepatomegaly, regression was defined as a reduction of at least 30 percent in the sum of the measurements below the xiphoid process and the costal margins. For hormonal assays, it was defined as a reduction of at least 50 percent in pretreatment abnormalities. If both tumor size and endocrine abnormalities were used as indicators, the response to treatment was determined on the basis of measurable tumor. Disease progression was defined as an increase of at least 25 percent in tumor measurements or the detection of new areas of malignant disease.

Statistical Analysis

Analysis of disease progression and survival was based on a proportional-hazards multivariate model, used to evaluate the relation of differences among treatment groups to characteristics of the patients and the disease.[6] Analyses of differences in rates of regression were modeled by multivariate linear logistic regression.[7] Unadjusted medians for the lengths of time to various events were estimated from Kaplan–Meier life-table curves,[8] and differences in time distributions that were not adjusted for patients' characteristics were evaluated with the log-rank test.[9] For the comparison of rates of toxicity and response to treatment, we used the Kruskal–Wallis exact test for ordered contingency tables.[10,11] For comparisons of patients' characteristics we used the R×C contingency-table exact test, which is similar to Fisher's exact test.[12] Only P values of less than 0.10 are reported. All tests were two-sided.

Results

Between November 1978 and June 1985, 125 patients were enrolled in this study. Eighteen patients were subsequently found to be ineligible (eight randomly assigned to receive chlorozotocin, seven to receive fluorouracil plus streptozocin, and three to receive doxorubicin plus streptozocin). An additional two patients withdrew from the study. Up-to-date follow-up information was available on all the remaining 105 patients, except 1 who was lost to follow-up after eight years. As Table 1 shows, the characteristics of the patients who could be evaluated were reasonably well balanced among the treatment groups.

Results of Treatment

Among the 105 eligible patients who underwent treatment, 3 did not have serial measurements adequate to determine their response. Results for the remaining 102 are shown in Figure 1. The overall differences in rates of regression among treatment groups are highly significant (P = 0.005). The doxorubicin–streptozocin group had significantly higher rates of regression than either the fluorouracil–streptozocin group (P = 0.05) or the chlorozotocin group (P = 0.002). The median durations of regression, measured from the start of therapy to the last observation of regression, were 17 months for chlorozotocin, 14 months for fluorouracil plus streptozocin, and 18 months for doxorubicin plus streptozocin. By an alternative measurement, from the first observation of regression to relapse, the median durations of regression were 21 months, 13 months, and 22 months, respectively. There was a larger number of patients with very long regressions (lasting two or more years) in the doxorubicin–streptozocin group (11 patients, vs. 4 in the chlorozotocin group and 2 in the fluorouracil–

streptozocin group). Six patients treated with doxorubicin plus streptozocin (17 percent) had regressions that persisted for more than four years, the longest of which lasted seven years and nine months.

Table 2 shows the relation of tumor regression to patient characteristics. Regression rates were higher for middle-aged patients (40 to 60 years of age), but this difference was only of borderline significance. There was no strong evidence that any specific type of endocrine abnormality made a patient either more responsive or more resistant to chemotherapy; the numbers were small, however.

Figure 2 shows the length of time to tumor progression. Doxorubicin plus streptozocin had a strong advantage in these terms over the other regimens ($P = 0.001$ for both comparisons), and this advantage was sustained over six years of observation. The P values remained unchanged after multivariate Cox regression analysis.

Survival times are compared in Figure 3. The chlorozotocin and fluorouracil–streptozocin groups had essentially the same survival times (median survival, 1.5 and 1.4 years). The patients who received doxorubicin plus streptozocin, however, had decidedly longer survival (median, 2.2 years); this survival advantage was even more striking in the long-term follow-up data. Table 3 shows survival in relation to a number of patient characteristics. Statistically significant predictors of survival included the ECOG performance score and age. The age effect was quadratic — i.e., patients from 40 to 60 years of age had longer survival times than older or younger patients. Survival differences among the treatment groups remained significant after adjustment for imbalances in these prognostic factors by the Cox regression analysis; that is, the doxorubicin–streptozocin regimen continued to be superior to the other two regimens in terms of survival ($P<0.01$ for both comparisons).

Table 1. Characteristics of the Study Patients.

Characteristic	Chlorozotocin	Fluorouracil + Streptozocin	Doxorubicin + Streptozocin
Sex (M/F)	13/20	20/14	18/20
Median age — yr (range)	57 (25–80)	51 (18–78)	53 (16–75)
Time from diagnosis			
<3 mo	24	22	19
3–<12 mo	3	6	14
≥12 mo	6	6	5
ECOG performance score			
0–1	23	24	27
2–3	10	10	11
Endocrine abnormality†			
Gastrin	4	11	11
5-HIAA	5	2	1
Hypercalcemia	2	2	3
Insulin	3	1	2
Corticotropin	1	4	1
VIP	2	1	1
Glucagon	1	1	2
None recorded	16	19	20
Indicator of response			
Tumor size	18	19	20
Hormone assay	2	3	2
Both	13	12	16

*The ECOG score is on a scale from 0 (fully active) to 4 (totally disabled).

†Nine patients had more than one endocrine-function abnormality. 5-HIAA denotes 5-hydroxyindoleacetic acid, and VIP vasoactive intestinal peptide.

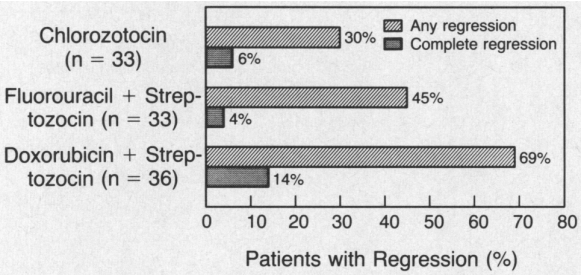

Figure 1. Rates of Tumor Regression, Measured Objectively, According to Treatment Group.

Thirty-one patients were crossed over to alternative therapy after their originally assigned treatment failed to induce regression. One of these did not have serial measurements adequate to determine response. Only 2 of 15 patients who could be evaluated had a regression with chlorozotocin after the previous failure of a streptozocin regimen; the same was true for only 3 of 15 patients who received a streptozocin regimen as secondary treatment. Regressions during secondary treatment were transient, persisting for a median of less than six months. The median interval to disease progression for all patients receiving secondary therapy was 4 months, and the median

Table 2. Response to Therapy According to Patients' Characteristics.*

Characteristic	No. of Patients	No. with Objective Regression (%)	P Value
Sex			
Male	50	26 (52)	
Female	52	24 (46)	NS
Age (yr)			
≤40	19	7 (37)	
>40–60	49	29 (59)	
>60	34	14 (41)	0.08
Time from diagnosis			
<3 mo	63	30 (48)	
3–<12 mo	23	14 (61)	
≥12 mo	16	6 (38)	NS
ECOG performance score			
0–1	72	38 (53)	
2–3	30	12 (40)	NS
Endocrine abnormality†			
Yes	47	23 (49)	
No	55	27 (49)	NS
Specific abnormality			
Gastrin	25	13 (52)	
5-HIAA	8	2 (25)	
Hypercalcemia	6	5 (83)	
Insulin	6	4 (67)	
Corticotropin	5	2 (40)	
VIP	4	2 (50)	
Glucagon	2	1 (50)	NS

*NS denotes not significant, 5-HIAA 5-hydroxyindoleacetic acid, and VIP vasoactive intestinal peptide. Objective regression was defined as regression measured objectively by the methods described in the text.

†Nine patients had more than one endocrine-function abnormality.

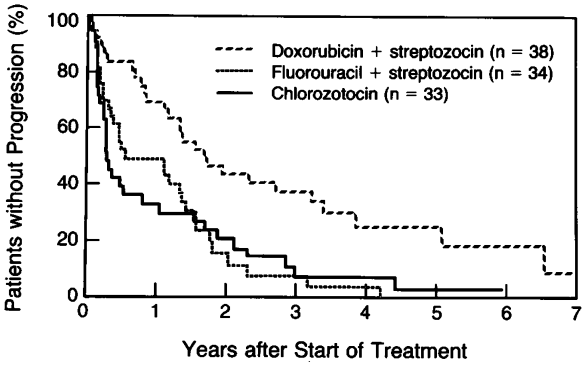

Figure 2. Length of Time to Disease Progression, According to Treatment Group.

P<0.001 for the comparison between doxorubicin plus streptozocin and fluorouracil plus streptozocin; P<0.001 for the comparison between doxorubicin plus streptozocin and chlorozotocin.

survival 12 months — both figures less favorable than with primary therapy.

Since the end results of this study depended on the evaluation of response, we studied the association of endocrine response and tumor-size response. Among 45 sets of adequate serial measurements of both tumor mass and endocrine abnormalities during primary or secondary treatment, 21 were recorded as indicating objective tumor regressions; 19 of these also showed a reduction in abnormal endocrine levels, and in one patient the endocrine level was unchanged. The only truly discordant results were in a patient who had a transient partial regression of malignant hepatomegaly (lasting four months) in association with a rising serum gastrin level.

Toxic Reactions

Toxic reactions to the first cycle of therapy are shown in Table 4, which is a composite of observations from both primary and secondary treatment. With regard to vomiting, the chlorozotocin regimen was distinctly more tolerable. This difference was more striking than Table 4 indicates, since nausea and vomiting associated with chlorozotocin generally occurred for only a few hours after the single-dose treatment. On the other hand, the two streptozocin regimens were usually associated with nausea or vomiting lasting through the entire five days of treatment. Stomatitis and diarrhea were essentially nonexistent in patients given chlorozotocin alone. Alopecia (data not shown) was almost universal with the regimen of doxorubicin plus streptozocin. The frequency of hematologic toxicity was roughly comparable among the three treatment groups. Thrombocytopenia was more frequent with chlorozotocin, and leukopenia was more severe with fluorouracil plus streptozocin. As is typical for agents containing nitrosourea, there was a definite tendency to increased hematologic toxicity with long-term chlorozotocin therapy. Heart failure developed in three patients, possibly as a consequence of doxorubicin toxicity; in the case of one of these patients, the maximal dose of 500 mg per square meter specified in the protocol was exceeded. There was one treatment-related death, of a patient treated with fluorouracil plus streptozocin who had severe leukopenia complicated by sepsis.

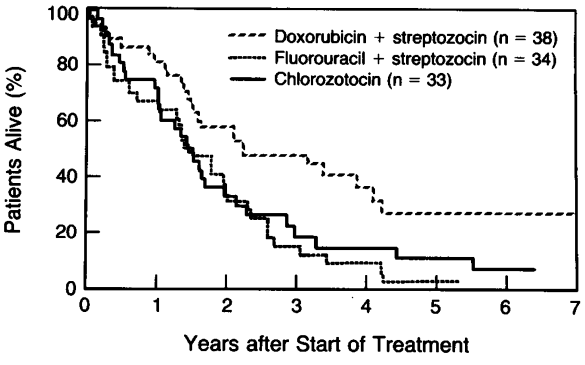

Figure 3. Survival, According to Treatment Group.

P<0.004 for the comparison between doxorubicin plus streptozocin and fluorouracil plus streptozocin; P<0.03 for the comparison between doxorubicin plus streptozocin and chlorozotocin.

Table 3. Length of Survival According to Patients' Characteristics.

Characteristic	No. of Patients	Median Survival (yr)	P Value*
Sex			
Male	51	2.0	NS
Female	54	1.5	
Age (yr)			
≤40	20	1.5	0.098
>40–60	50	2.1	
>60	35	1.3	
Time from diagnosis			
<3 mo	65	1.6	NS
3–<12 mo	17	1.8	
≥12 mo	23	1.6	
ECOG performance score			
0–1	74	2.1	0.002
2–3	31	1.0	
Endocrine abnormality			
Yes	49	2.0	
No	56	1.6	NS

*NS denotes not significant.

Nephrotoxicity was in most cases limited to a mild increase in serum creatinine. Nine patients had severe chronic renal insufficiency, however. Seven of them had azotemia requiring dialysis; two, both treated with streptozocin regimens, had severe Fanconi's syndrome. Since in many patients in this study the disease did not respond to treatment and they therefore had only short exposures to chlorozotocin or streptozocin, the figures in Table 4 undoubtedly underestimate the potential of these agents for causing chronic renal damage. Among the patients who received chlorozotocin, there was a clear relation between the total dose and chronic nephrotoxicity. No patient who received a total dose of 750 mg of chlorozotocin per square meter

Table 4. Toxic Reactions According to Treatment Group.

Toxic Reaction*	Chlorozotocin (N = 51)	Fluorouracil + Streptozocin (N = 42)	Doxorubicin + Streptozocin (N = 44)
		percent	
Vomiting			
Any	43	81	80
Severe	2	41	20
Stomatitis			
Any	0	19	5
Severe	0	5	0
Diarrhea			
Any	6	33	5
Severe	0	2	0
Leukopenia†			
$<4\times10^9$ cells/liter	53	56	57
$<2\times10^9$ cells/liter	14	25	5
Thrombocytopenia†			
$<100\times10^9$ cells/liter	22	8	0
$<50\times10^9$ cells/liter	6	6	0
Creatinine elevation‡			
>0.03 mg/dl	32	29	44
>1.0 mg/dl	15	7	2
Chronic renal insufficiency	7	7	4

*For vomiting, stomatitis, diarrhea, leukopenia, and thrombocytopenia, the results are for the first course of therapy only. The values for creatinine elevation are for all courses. Only the patients who had adequate documentation of toxic reactions are included.

†Only patients for whom adequate serial measurements were available are included.

‡To convert values for creatinine to millimoles per liter, multiply by 88.4.

or less had this complication, whereas 20 percent of those who received 751 to 1000 mg per square meter and 56 percent of those who received more than 1000 mg per square meter had chronic renal failure.

Discussion

Advanced islet-cell carcinoma has proved to be surprisingly sensitive to a variety of cytotoxic drugs — a sensitivity not shared by other neuroendocrine cancers.[13] Streptozocin seems to have a specificity for this neoplasm, and we have observed a progressive increase in therapeutic effectiveness as we have moved from streptozocin alone to streptozocin plus fluorouracil and then to streptozocin plus doxorubicin. This effectiveness seems to be substantial, resulting in palliation of endocrine syndromes and, most important, improved survival. The duration of tumor regression and of improvement in endocrine syndromes was in the main relatively long, with a median of 1.5 years and a maximum of almost 8 years.

Although the combination of streptozocin and doxorubicin was the most effective, streptozocin produced frequent and often severe nausea and vomiting, which compromised both the patients' quality of life and their compliance. Chlorozotocin was found to have therapeutic activity comparable to that of streptozocin plus fluorouracil, with considerably less emetic effect and more convenience in administration. This agent seems attractive as a possible replacement for streptozocin in combination regimens. Other agents with apparent activity in islet-cell carcinoma that have not yet been evaluated in randomized trials include dacarbazine and interferon alfa.[14,15]

In the past we have continued chemotherapy indefinitely in patients who have achieved an objective tumor regression, a practice that can be trying for patients and that sometimes leads them to abandon therapy. In addition, such a policy can result in irreversible chronic renal failure requiring dialysis. Future studies should examine the possibility of continuing therapy only until the disease has stabilized, with maximal tumor regression. Considering the usual slow rate of growth of islet-cell tumors, such an approach may allow patients more freedom from the stress of therapy before the malignant disease advances to the point at which the resumption of therapy is justified.

Clearly, islet-cell carcinoma is responsive to chemotherapy, but the chance of long-term survival with current regimens remains small. There is strong justification for continued clinical research into this rare disease.

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