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Phase II Study of Chlorozotocin in Islet Cell Carcinoma

A Southwest Oncology Group Study

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Summary. *Seventeen patients with islet cell carcinoma received chlorozotocin (CTZ). Nine received 200 mg/m² IV every 6 weeks and 8 received 100 mg/m². Responses were seen in eight (2 complete, 5 partial, 1 minor) of 13 patients who had received no prior chemotherapy, and in zero of four who had received prior chemotherapy. Toxicity was mild in most patients and consisted predominantly in myelosuppressions; however, in one patient severe renal failure developed. CTZ may have activity comparable to streptozotocin in this group of patients.*

Introduction

Neoplasms of the pancreatic islet cells may be quite protean in their presentation, and provide a therapeutic challenge to both surgical and medical oncologists. Two unique features of these neoplasms are clinical manifestations of endocrine hyperfunction in approximately 20% of patients [7], and a usually indolent clinical course in most instances. Surgical management, with curative resection, can usually be accomplished at an early stage with functioning tumors such as insulinomas and gastrinomas. For patients whose symptoms are uncontrolled or whose course indicates a more aggressive malignant disease, chemotherapy is often considered.

Initial experiences with these neoplasms demonstrated favorable responses to 5-fluorouracil (5-Fu) [8], streptozotocin [2], and tubercidin [1]. A recent study by the Eastern Cooperative Oncology Group [9] compared the effects of streptozotocin (STZ) and of STZ combined with 5-Fu in a randomized fashion. In 84 evaluable patients, the combination produced a response rate of 63%, versus 36% for STZ alone. A survival advantage for the combination was also seen (26 vs 16.5 months) but was not statistically significant. The predominant toxicity seen was nausea and vomiting in 84% of patients, being severe in one-third. It appears that STZ is the most active single agent in this group of patients, but that gastrointestinal toxicity is substantial, limiting its long-term usefulness.

Chlorozotocin (CTZ) is a chloroethyl analog of STZ and is described chemically as 2-3(2-chloroethyl)-3-nitrosoureidol-D-glucopyrarose. It was synthesized by Johnston [6], and produces alkylation and crosslinking of DNA [3]. Its predominant toxicity is myelosuppression, with nausea and vomiting being minimal [4, 5]. Because of its structural similarity to STZ, and the activity of this latter agent in islet cell carcinoma, the Southwest Oncology Group undertook a phase II evaluation of CTZ in patients with this neoplasm. The purpose of this paper is to report this experience.

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Materials and Methods

All patients were required to have biopsy-proven islet cell carcinoma not amenable to surgical resection. Pathologic review of histologic material was not performed. Because of the indolent nature of these tumors, patients were placed on study only if they had significant symptoms or disability from their disease, or there was evidence of rapidly advancing malignant disease. Patients receiving prior chemotherapy (including STZ) and radiotherapy were eligible, but therapy was delayed 4–6 weeks or until any toxicity cleared.

All patients were required to have either objectively measurable disease on physical examination, X-ray study, liver scan, or CAT scan, or a significant biochemical abnormality specific for their tumor, e.g., elevated insulin level. Normal hematologic status (WBC $\geq 4{,}000/mm^3$ and platelets $\geq 100{,}000/mm^3$) and adequate renal function (BUN ≤ 25 mg%, creatinine < 2.0 mg%) were required.

All patients received CTZ at intervals of 6 weeks. The drug was reconstituted with sterile water and administered by rapid IV injection. Patients were divided into good and poor risks, with the dose levels being 200 mg/m² and 100 mg/m², respectively. Poor risk was defined as presence of either a serum creatinine of ≥ 1.5 mg%, serum bilirubin ≥ 2.0 mg%, or poor tolerance to prior chemotherapy.

Doses of CTZ during subsequent courses were adjusted for hematologic and renal toxicity. If the white blood cell nadir was $> 4{,}000/mm^3$ and platelet nadir $> 100{,}000/mm^3$ the dose was increased by 10%. If either the white blood cell nadir was $< 2{,}000/mm^3$ or platelets $< 50{,}000/mm^3$ the dose was decreased by 25%. If severe hematologic toxicity (WBC $< 1{,}000/mm^3$ or platelets $< 25{,}000/mm^3$) the dose was decreased by 50%. If deterioration of renal function occurred (BUN > 30 mg% or creatinine > 2.0 mg%) CTZ was discontinued until these returned to adequate levels. In the presence of minor proteinuria (trace or 1+) without deterioration of renal function, therapy was continued. Treatment with CTZ was continued in the presence of either a response or stable disease, or until progressive disease was documented.

During therapy all measurable parameters (objective or biochemical) were studied every 6 weeks. Complete blood and platelet counts were obtained every 2 weeks. BUN, creatinine, bilirubin, SGOT, LDH, blood sugar, and alkaline phosphatase were obtained every 6 weeks.

In patients with objectively measurable disease, a complete response (CR) was defined as disappearance of all clinical evidence of tumor for a minimum of 6 weeks. A partial response (PR) consisted of a 50% or greater decrease in the sum of the products of the diameters of measured lesions for a minimum of 6 weeks. In patients in whom malignant hepatomegaly was the indicator, a 30% reduction in the sum of the measurements below the xiphoid and right and left costal margins was required. Stable disease was defined as a steady state, and a minor response (MR) as insufficient regression to qualify as a partial regression for 12 weeks or more. Progressive disease consisted of an increase of at least 50% in the size of measurable lesions or a 30% increase in liver measurements. Finally, relapse was defined as the appearance of new lesions or the reappearance of old lesions in patients who have had a complete remission, or a 50% or greater increase in the products of the diameters of measurable lesions.

In patients with endocrine hyperfunction, normalization of the tumor product was considered a complete response. A reduction by at least 50% compared to pretreatment levels was a partial response, and an increase by 50%, progression.

Results

Nineteen patients were registered, and 17 are evaluable for response and toxicity. In the two inevaluable patients, a major protocol violation occurred in one because of administration of a second chemotherapeutic agent, and in the other insufficient data were submitted. The clinical characteristics and response data for the 17 evaluable patients are presented in Table 1. Eleven had received no prior therapy, two prior radiotherapy only, and four prior chemotherapy with or without radiotherapy. Nine patients received CTZ 200 mg/m^2, and eight patients, 100 mg/m^2. The median age was 56 years (range 30–72) and the M/F ratio, 9/8. Eight of 17 had functioning tumors and in one instance multiple products were seen (gastrin, pancreatic polypeptide). Responses occurred in 7 of 17 patients (CR 2, PR 5), and in one patient a minor regression was seen. In the three patients with functioning tumors, amelioration of symptoms (diarrhea and hypoglycemia) occurred coincidentally with the biochemical responses. There were no obvious differences in response rates between liver metastases and abdominal masses, with responses occurring to equivalent degrees in both areas. If only patients not receiving prior STZ are considered, seven of 13 (54%) responded, and one of 13 have demonstrated minor responses. Four of nine patients receiving 200 mg/m^2 and three of eight receiving 100 mg/m^2 responded. The median duration of the partial and complete responses is 12.0+ months (range 3.9–16.0+). Five of 17 patients have expired and the median projected survival for the group is 17.0+ months (Kaplan-Meier survival curve). Median survival of nonresponding patients is 13.0 months, and that for responders will be in excess of 18.0 months. This difference is, however, not statistically significant ($P = 0.19$) at this time.

All patients had objectively measurable tumor, and eight demonstrated biochemical abnormalities specific for their neoplasm. All responses consisted of objective tumor regressions plus a decrease in tumor product (if present) of greater than 50% of pretreatment values. Toxicity of CTZ in this group was moderate. Leukopenia (WBC $\leq$ 3,000/mm^3) was seen in nine of 17 patients, being severe ($<$ 2,000/mm^3) in three. Thrombocytopenia (platelets $<$ 100,000/mm^3) occurred in five of 17 patients, and was severe ($<$ 25,000/mm^3) in one instance. Gastrointestinal toxicity was mild, with only five of 17 patients experiencing mild nausea and/or vomiting. Mild neurologic toxicity consisting in paresthesias, incoordination,

Table 1. Clinical and response data

Patient no.	Age/ Sex	Dose level CTZ (mg/m^2)	Previous therapy[a]	Functional status[b]	Response[c]	Duration of response (months)	Survival (months)
1	56/F	200	None	NS	PR	16.0+	24.0+
2	36/F	200	None	NS	NR	–	18.0+
3	55/M	200	None	NS	PR	5.0	22.0+
4	60/M	200	5-FU, ADR, STZ, Tuber	VIP	NR	–	2.0+
5	37/M	200	None	Gastrin	NR	–	24.0+
6	39/F	200	None	Insulin	PR	12.0+	16.0+
7	63/M	200	None	Gastrin	NR	–	12.0+
8	48/F	200	XRT	NS	NR	–	10.0
9	57/M	200	None	NS	CR	11.0	14.0+
10	70/M	100	None	NS	NR	–	13.0
11	70/F	100	XRT	NS	MR	–	26.0+
12	30/M	100	XRT, 5-FU, STZ	NS	NR	–	3.0
13	65/F	100	None	VIP	PR	12.0+	18.0+
14	65/M	100	None	NS	CR	14.0+	16.0+
15	72/M	100	None	Insulin	PR	3.0	5.0
16	53/F	100	5-FU, STZ	Gastrin, pancreatic polypeptide	NR	–	11.0
17	72/F	100	STZ	Gastrin	NR	–	10.0+

[a] 5-FU, 5 fluorouracil; ADR, adriamycin; STZ, streptozotocin; Tuber, tubercidin; XRT, radiotherapy
[b] NS, nonsecretory
[c] CR, complete response; PR, partial response; MR, minor response; NR, no response

and hallucinations was reported in two patients and was transitory. All these patients had received prior STZ. Mild pulmonary dysfunction, reflected in a decrease in the DL_{CO} of 40% with a normal chest X-ray, was noted in a single patient. No clinical symptoms were reported in this instance. Finally, renal toxicity in the form of elevations of BUN (> 25 mg%) or creatinine (> 1.5 mg%) was seen in three patients, being severe and delayed in onset in one instance. This last patient eventually required hemodialysis, with renal failure remaining irreversible. The cumulative dosage of CTZ was examined to determine whether severe renal failure could be dose-related. The patient with severe renal toxicity received a total of 1,200 mg/m^2; however, two other patients received dosages in excess of this (1,390 mg/m^2, 1,445 mg) without developing abnormalities of their BUN and creatinine.

Discussion

The results of this study indicate that chlorozoticin has activity in patients with islet cell carcinoma which may be equivalent to that of STZ. No responses in the small group of patients who had received prior STZ was found, but in 13 patients with no prior chemotherapy a response rate of 46% (6 of 13) was seen. This may be equivalent to that reported recently with STZ (36%) by the ECOG [6], but the small size of the present group makes this comparison difficult. Additionally, responses occurred in patients receiving either dose level of CTZ. The toxicity produced by CTZ was moderate and was predominantly myelosuppression; however, the presence of severe renal toxicity in one patient is disturbing. The lack of significant gastrointestinal toxicity, and the possibility that CTZ may be equivalent to STZ in overall activity indicate that further trials of CTZ should be performed in this patient group. Careful monitoring of renal function will be required in these trials. Finally, since responses occurred with both dose levels of CTZ, combinations of this agent at the lower dose level with 5-Fu should be possible, and may result in improved efficacy. This study is now in progress in the Southwest Oncology Group.

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