

## Original article

# Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282

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\*See Appendix on page 1142 for participating institutions

### Summary

**Background:** A phase II study of dacarbazine (DTIC), was conducted to determine the response rate, duration of response, toxicity and overall survival of patients with advanced pancreatic islet cell tumors.

**Patients and methods:** Fifty patients with advanced pancreatic islet cell tumors, having progressive symptoms or evidence of rapidly advancing disease were entered on this study. DTIC was given by IV infusion at a dose of 850 mg/m<sup>2</sup>, over 60–90 minutes, repeated every four weeks.

**Results:** The response rate was 33% in 42 patients who had measurable tumor, and 34% in the 50 patients (90% confidence

interval (90% CI): 23%–47%). The majority of the responses were seen in patients without prior chemotherapy. Median overall survival was 19.3 months. There were two lethal toxicities on the study, one septic shock and one myocardial infarction. Grade 4 toxicities were, hematological (5 patients), sepsis, neurological (depression and paranoid behavior) and bleeding (1 patient each). The most common toxicity was vomiting, grade 3 in 13% of patients.

**Conclusions:** DTIC has activity in advanced previously untreated pancreatic islet cell tumors.

**Key words:** dacarbazine, islet cell tumors, pancreas, phase II

### Introduction

Pancreatic islet cell tumors are a rare group of neoplasms. These tumors have a neuroendocrine origin, and have the ability to synthesize various peptide hormones by amine precursor uptake and decarboxylation (APUD) [1]. Aggressive surgical resection is the treatment of choice in resectable tumors. The clinical course of advanced tumors is variable, with most patients initially having an indolent course not requiring pharmacologic therapy. After a period of slow growth, many of these tumors show an aggressive behavior requiring intervention. In patients with bulky liver metastasis, surgical debulking of liver metastasis or chemoembolisation may result in palliation. In patients with hormone hyperfunction syndromes, octreotide, a synthetic octapeptide, is effective in control of symptoms [2]. Chemotherapy is frequently used for symptomatic patients with advanced tumors who have progressive disease. Agents with activity in this disease are 5-fluorouracil (5-FU), streptozocin, chlorozotocin and doxorubicin [3–5]. Combination chemotherapy with streptozocin and doxorubicin results in higher response rates and improved survival compared to single agent therapy, but at the expense of increased toxicity [6]. Dacarbazine (DTIC, NSC-45388) is a non-classic synthetic alkylating agent [7]. It has single agent activity in metastatic malignant melanoma, Hodgkin's disease, sarcomas, childhood neuroblastoma

and primary brain tumors. The common side effects of this drug are myelosuppression and vomiting [8]. We evaluated the activity of DTIC in pancreatic islet cell tumors, as preliminary reports indicated this to be an active agent. [9, 10]. In one report, therapy with DTIC resulted in 3 of 5 patients having a biochemical or objective response [9], and in the other study 5 of 10 patients had an objective response [10].

### Patients and methods

#### Study schema

The Eastern Cooperative Oncology Group (ECOG) opened a two-armed crossover study of DTIC and cisplatin in patients with advanced, unresectable islet cell carcinoma. Because of early toxicities on the cisplatin arm, it was subsequently terminated and the cross over design eliminated. By that point in time only two patients received cisplatin as induction treatment and another four received cisplatin on crossover. This report is an analysis of DTIC treatment for patients with islet cell carcinoma, which was the primary focus of the study.

#### Patients

To be eligible for this protocol, patients had to have histologically confirmed unresectable islet cell carcinoma with measurable malignant disease to serve as an objective indicator of response to therapy. For patients without clearly measurable tumor, measurements of endocrine hyperfunction served as objective indicators of response. Patients had

progressive symptoms resulting from their malignant disease or evidence of rapidly advancing disease. Laboratory measurements had to be adequate (White cell count (WBC)  $> 4000/\text{mm}^3$  and platelet  $> 130,000/\text{mm}^3$ ), and ECOG performance status was 0–3. Patients could not enter the study within three weeks after a major surgical procedure, or within two weeks of an exploration or biopsy. Prior radiotherapy to the primary area of measurable disease, and chemotherapy or radiotherapy one month prior to study entry were not allowed. Patients with active infectious process and severe malnutrition were ineligible. No other concomitant cancers were allowed. The protocol was approved by the human investigations committee at each site and informed consent was obtained from all patients to participate in the study.

#### Treatment plan

The DTIC treatment was given at the dose of  $850 \text{ mg}/\text{m}^2$  by i.v. infusion over 60–90 minutes on day one, repeated every four weeks. Antiemetic treatment with phenothiazines was allowed.

#### Dose modifications

Dose modifications for hematologic toxicities were based on nadir counts. If the WBC decreased to below  $2000/\text{mm}^3$  and/or the platelet count decreased to below  $75,000/\text{mm}^3$ , there was a 25% reduction in dose. If the WBC decreased to below  $1000/\text{mm}^3$ , and/or the platelets decreased to below  $25,000/\text{mm}^3$ , there was a reduction of 50% in dose. Treatment was to be given for at least two courses, if possible, and to be continued until progression occurred.

#### Measurement of effect

The principal endpoints of the study were 1) tumor response, 2) toxicity, 3) survival, and 4) duration of response. Complete response was defined as absence of any clinically detectable tumor mass and absence of any laboratory detectable evidence of endocrine hyperfunction. Partial response was defined as a reduction of at least 50% of the product of the longest perpendicular diameters of the most clearly measurable mass lesion. If hepatomegaly was the prime indicator, then there had to be a reduction of the sum of liver measurements below costal margins of at least 30%. In addition there could be no increase in any other indicator lesion and no new areas of malignant disease. Performance status could not decrease by more than one level (or to performance status 4) and weight loss could not be more than 10% in order for the response to be still considered partial response. Objectively stable disease was defined as regression not large enough to meet the criteria of partial response, and less than 25% increase in any measurable lesion, no new areas of malignant disease, and no significant deterioration in weight symptoms or performance status. Objective progression was defined as an increase in any measurable lesion of more than 25% or significant deterioration in symptoms or decrease in weight or performance status.

If endocrine hyperfunction was employed as the indicator of response, improvement in at least one of the following criteria had to be met: 1) Zollinger–Ellison syndrome, ACTH production, Urine 5HIAA and Glucagonoma: a reduction of hormonal levels by at least 50% compared to pretreatment levels. 2) Insulinoma: a reduction of elevated blood insulin levels to normal range and freedom from hypoglycemia symptoms without glucose supplementation. 3) Pancreatic cholera: a reduction of fecal volume and/or weight by at least 75% with a return to normal of all associated electrolyte abnormalities.

#### Statistical considerations

The study was designed so that if the true response rate was 30%, then with 90% probability (or greater) the observed response rates were to be between 15% and 45%. Kaplan–Meier curves were calculated for

overall survival, and for survival by baseline characteristics. Log-rank tests were done to compare survival between groups based on patient characteristics. Predefined risk factors for progression were examined whether they predicted response, using a Fisher's exact test. These risk factors were: 1) creatinine level:  $< 1.5 \text{ mg}/\text{dl}$  or  $> 1.5 \text{ mg}/\text{dl}$ ; 2) performance status. ECOG 0/1 or ECOG 2/3; 3) functional status: functioning or non-functioning, 4) objective indicator: measurable tumor or non-measurable tumor/endocrine hyperfunction; 5) previously treated. no or yes.

## Results

### Patient accrual

A total of 54 patients entered this study between April 1983 and September 1989. Two patients were excluded from the analysis since they were initially randomized to the cisplatin arm and another two patients were excluded on pathologic review. Sixteen ECOG institutions contributed patients to this study (see Appendix).

Table 1 summarizes the characteristics of the 50 analyzable patients. All but three patients were white, and distribution was about equal between males and females. Forty-two patients (84%) had measurable tumor, 8 (16%) patients had creatinine level  $> 1.5 \text{ mg}/\text{dl}$ , 8 (16%) pa-

Table 1 Patient characteristics.

Characteristic	Patients <i>n</i> = 50 (%)
Creatinine	
< 1.5 mg/dl	42 (84)
$\geq 1.5 \text{ mg}/\text{dl}$	8 (16)
Performance status	
0–1	42 (84)
2–3	8 (16)
Functional Status	
Functioning	24 (48)
Non functioning	26 (52)
Objective indicator	
Measurable tumor	42 (84)
Endocrine function only	8 (16)
Sex	
Male	24 (48)
Female	26 (52)
Age	
Mean	53.8
Range (years)	23–75
Race	
White	47 (94)
Black	3 (6)
Previous surgery	
No	12 (24)
Yes	38 (76)
Previous chemotherapy	
No	28 (56)
Yes	22 (44)

tients had performance status 2 or 3, 24 (48%) had endocrine hyperfunction and 22 (44%) had previous chemotherapy.

#### Antitumor activity

The response rate in 50 evaluable patients according to study criteria was 34% (90% CI: 23%–47%). In 42 patients with measurable tumor, the response rate was 33%. In the 50 patients there were 4 complete responses and 13 partial responses (Table 2). Onset of response was between one month after treatment was started and 17 months. Median response duration was 10 months (range 4–28 months). Time from randomization to relapse was 7–39 months. There were only 3 responders, response rate 13.6%, (90% CI: 4%–32%) in 22 patients with previous chemotherapy. In untreated patients the response rate was 50% (90% CI: 33%–67%) with 14 responders in 28 patients ( $P = 0.008$ , Fishers exact test). No other difference in baseline patient characteristics between the group of patients who responded and did not respond was significant.

#### Survival

Median survival overall was 19.3 months. Median survival among the responders was 42 months (range 12–81 months). Median survival for males was higher than females ( $P = 0.016$ , log-rank test), for patients with creatinine levels less than 1.5 mg % ( $P = 0.03$ , log-rank test), for patients with a better performance status ( $P = 0.012$ , log-rank test), and for patients with no previous chemotherapy ( $P = 0.0045$ , log-rank test). No other significant differences in survival by baseline characteristics groups were observed. The median survival of patients with performance status ECOG 2 or 3 was only 1.7 months.

#### Toxicity

Since DTIC was administered to 54 patients, toxicity data is provided for all 54 patients, including the two patients who crossed over from cisplatin and received DTIC and the two ineligible patients. A summary of the toxicities (ECOG toxicity criteria) is given in Table 3. A total of 16 patients (30%) had grade 3–4 toxicities. Apart from 5 grade 4, hematological toxicities, the most common toxicity was vomiting, with 7 grade 3 and 26 grade 2 cases. There were two lethal toxicities on the study. One patient had septic shock on day 15, cycle 1, and another patient had a myocardial infarction. The patient who had sepsis also had a grade 4 hematologic toxicity (platelet  $17,000/\text{mm}^3$  and WBC  $1,200/\text{mm}^3$  on day 15, cycle 1). There were three grade 4 non-hematological toxicities, one case of sepsis, one case of depression and paranoid behavior with an unclear cause, and one case of bleeding without thrombocytopenia.

Table 2. Objective response.

	Total	%
Cases analyzed	52	100
Unevaluable	2	3.8
Complete response	4	8.0
Partial response	13	26
Response rate	–	34

Table 3. Treatment related toxicities (ECOG toxicity criteria).

Toxicity	Grade			
	1	2	3	4
Gastrointestinal	6	0	0	0
Vomiting	11	26	7	0
Diarrhea	7	4	0	0
Infection	3	3	1	1
Bleeding	1	0	0	1
Skin/Mucosa	7	2	1	0
Neurologic	11	6	1	1
Respiratory	3	0	1	0
Genitourinary	11	4	0	0
Hematologic	11	8	4	5
Liver	1	2	0	0
Other <sup>a</sup>	17	7	2	0

<sup>a</sup> Other included fever, chills, alopecia, cardiac, edema, anorexia, sweats, fatigue, ascites, gastric ulcer, abdominal disc, headache and weight gain. There were two grade 5 (lethal) toxicity's on study. One patient had a myocardial infarction and another sepsis.

#### Discussion

This phase II study, is the largest experience of DTIC in pancreatic islet cell tumors. The main toxicities observed were hematological and vomiting. Most patients had some degree of vomiting, and a severe degree was observed in 13%. Phenoazines were used for control of nausea and vomiting in this study, serotonin type 3 (5HT<sub>3</sub>) antagonists such as ondansetron, granisetron and dolasteron were not available at that time. As DTIC is classified as a highly emetogenic agent, patients receiving treatment in the present time would be given a 5HT<sub>3</sub> antagonist combined with steroids, which should result in better control of emesis.

The combination of streptozocin and doxorubicin reported by Moertel et al. [6], can still be considered the best regimen in terms of response and overall survival for previously untreated patients with islet cell tumors. This study randomized 105 patients with advanced islet cell carcinomas to streptozocin plus fluorouracil, streptozocin plus doxorubicin or chlorozotocin alone. The response rate (63%) and median survival (26.4 months) for the combination of streptozocin plus doxorubicin was significantly superior to the other two regimens.

However, the regimen of streptozocin and doxorubicin resulted in severe degree of vomiting in 20% of patients. This regimen was also nephrotoxic with chronic renal insufficiency developing in 9% of patients. No new developments have taken place since the publication of this study by Moertel et al. in 1992, and even now streptozocin and doxorubicin are commonly used to treat pancreatic islet cell tumors.

Both carcinoid and pancreatic islet cell tumors share a common origin from neuroendodermal cells and may be expected to respond similarly to chemotherapeutic agents. However, DTIC appears to have a lower response rate in carcinoid tumors. The Southwest Oncology Group (SWOG) conducted a study of DTIC in 56 evaluable patients with previously untreated carcinoid tumors [11]. The response rate was 16% (95% CI: 8%–28%), median survival 20 months, and the SWOG concluded that DTIC had minimal activity. The toxicity seen was similar to our study with severe vomiting in 18%.

It is unfortunate that progress has not been made over the last decade. Studies with carboplatin, mitoxantrone, and modulation of 5-fluorouracil by interferon have shown disappointing results [12–15]. There is a need to develop and evaluate new treatments, however it is surprising that newer drugs such as the taxanes (paclitaxel, docetaxel), topoisomerase inhibitors (irinotecan, topotecan), platinum compounds (oxaliplatin) and gemcitabine have not been tested in this group of cancers.

Even though DTIC appears to have activity, its role in the treatment of pancreatic islet cell tumors is unclear. The combination of streptozocin and doxorubicin remains the best regimen for patients with a good performance status. It is doubtful that patients who have a performance status of EGOG 2 or more, receive any benefit from chemotherapy. In our study the median survival was a dismal 1.7 months and consideration should be given to exclude these patients from future studies. Our study, which was designed in 1982, similar to most other published trials in neuroendocrine tumors had outmoded entry and assessment criteria. Future studies should assess response in those only with measurable tumor and restrict eligibility to those with normal organ function and a good performance status. No agent appears to be active as second line therapy of pancreatic islet cell tumors, and these patients should be treated on clinical protocols. As carcinoid and pancreatic islet cell tumors are relatively uncommon, large multi institutional or cooperative group efforts are needed to improve the survival of these patients. By publication of this manuscript the authors hope to stimulate discussion in the clinical research community for newer therapies.

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#### \*Appendix: Participating institutions

Albany Medical College; Case Western Metro. Health Medical Center, Fox Chase Cancer Center; Hospitals of the University of Pennsylvania; Mayo Clinic; New England Medical Center; New York University Medical Center; Northwestern Medical Center; Rochester School of Medicine; Roswell Park Memorial Institute; Rush Presbyterian, St. Lukes; Twin Tiers CCOP – Lourdes Hospital; Tulsa CCOP; University of Minnesota, VA Hospital; University of Pittsburgh, University of Wisconsin.

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