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Metastatic Carcinoid and Islet Cell Tumours of the Pancreas: a Phase II Trial of the Efficacy of Combination Chemotherapy with 5-Fluorouracil, Doxorubicin and Cisplatin

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A phase II trial of chemotherapy in carcinoid and islet cell pancreatic tumours has been conducted with the FAP protocol: 5-fluorouracil 400 mg/m² per day (5-FU) for 3 days, 50 mg/m² doxorubicin on day 2, and 90 mg/m² cisplatin on day 2, repeated every 4 weeks. 24 patients, 20 non-pretreated and 4 pretreated, were included. For non-pretreated patients we observed 1 complete response and 2 partial responses. The response rate was 15% (95% confidence interval 0–31%). No response was observed in the pretreated patients. The toxicity was mainly digestive and haematological with 7 patients experiencing vomiting grade 3 and 3 patients with leucopenia grade 3. We conclude that the FAP protocol is of poor efficiency in endocrine tumours.
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INTRODUCTION

CARCINOID AND islet cell pancreatic tumours are rare, representing 1% of all neoplasms [1]. They are thought to be of neuroectodermal origin, associated with the APUD (amine precursor uptake and decarboxylation) cell system. Timing of the diagnosis depends very much on the site of the primary and the existence of a functional syndrome. Surgery remains the treatment of choice for localised disease leading to cure at this stage. Even when distant metastases are present, even incomplete surgical excision of the tumoral tissue may offer good palliation, as these tumours are often slowly growing [2].

Nevertheless, when surgery is not feasible, and when the disease is evolutive and symptomatic, medical treatment has to be considered. At this point the mean survival expectancy is reduced and in the range of 2–3 years [2]. Chemotherapy efficacy has been seldom reported, and the most efficient association seems the combination of 5-fluorouracil (5FU) and streptozotocin, which gives a 33% response rate [2]. Some data favour the efficacy of 5-FU and doxorubicin [3] and in one study the combination of doxorubicin and cisplatin has obtained a partial response in 3 of 6 patients [4]. Combination chemotherapy with 5-FU, doxorubicin and cyclophosphamide [5, 6] associated or not with streptozotocin has demonstrated some efficacy, with a response rate of 35%. Responses, however, have been of short duration and only rarely complete.

As more effective combinations are needed, we have conducted a phase II trial with the combination of 5-FU, doxorubicin and cisplatin (the FAP protocol) in the hope to achieve a response rate higher than 30%.

PATIENTS AND PROTOCOL

Between 1982 and 1988, 24 patients were treated with the FAP protocol for carcinoid or islet cell pancreatic tumours (Table 1).

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Inclusion criteria were histologically proven carcinoid or islet cell pancreatic tumour, with distant metastasis, non-surgically curable, and with clearly evolutive distant metastasis. There were 24 patients included in the trial: 9 women and 15 men, median age 50 (range 20 to 68) years. 20 patients received no prior chemotherapy. There were 18 carcinoid tumours. Primary sites were the small intestine (4 cases); the rectum (1); the lung (5); or unknown (5). There were 6 pancreatic islet cell tumours (non-secreting advanced tumours).

The main tumoural localisations were the liver in 19 cases; adbominal or peripheral lymph nodes in 10; bones in 5; the peritoneum in 4 and the pancreas itself in 5 cases. A carcinoid syndrome was present in 13 out of the 19 patients with carcinoid tumour (diarrhoea in 11 cases and/or flushes in 9 cases). Elevation of 5-hydroxyindole acetic acid (5-HIAA) was noted in 16 out of these patients.

Most of the patients were in good condition: 13 (54%) were WHO grade 0–1, 9 grade 2 and 2 grade 3.

The FAP protocol of chemotherapy consisted of 5-FU 400 mg/m² per day in 1 h perfusion on days 1, 2 and 3, doxorubicin 50 mg/m² intravenous bolus on day 2 and cisplatin 90 mg/m² in 1 h perfusion with hydration on day 2. Cycles were repeated every 4 weeks in the absence of severe toxicity or tumour progression. The response rate and toxicity were analysed according to the WHO criteria.

RESULTS

All 24 patients included in this phase II trial were evaluated for tumoral response and toxicity.

The median number of cycles of chemotherapy was 4 (range: 1–10). 2 patients decided to stop treatment after two cycles, when they were stabilised but had a poor tolerance and a bad quality of life under chemotherapy. In the group of patients treated with FAP as first-line therapy (non-pretreated patients, $n = 20$) we observed a 15% response rate (S.E. 0–31%) with 1 complete response (5%) lasting 20 months and 2 partial responses lasting 9 months. 12 patients (60%) had stable disease for a median time of 5 (2–24+) months, and 4 (20%) had progressive disease which lead to rapid interruption of the protocol. There was no difference

Table 1. Patients' characteristics: carcinoid and metastatic islet cell tumours treated with combined chemotherapy (FAP protocol)

Patients	(sex, age)	Primary site	Histology	Carcinoid syndrome	Metastases sites	Status (WHO)	5-HIAA*	Tumour response and duration	5-HIAA evolution	Carcinoid syndrome evolution	No. of cycles	Survival and second-line treatment
Non-pretreated patients												
1	(M, 51)	Lung	Carcinoid	0	L	3	146	PR, 9 mo	↘	–	6	Dead at 10 mo
2	(M, 42)	Unknown	Carcinoid	0	N	2	<20	CR, 20 mo	–	–	9	Dead at 33 mo after SLT
3	(M, 58)	Rectum	Carcinoid	0	L+B	2	<20	SD, 3 mo	–	–	3	Dead at 12 mo after SLT
4	(M, 58)	Small int.	Carcinoid	+	L+N	2	77	PD	↘	NC	5	Dead at 8 mo
5	(F, 37)	Pancreas	Islet cell	0	L+N+Lu+O	2	<20	PR, 9 mo	–	–	5	Dead at 9 mo—cerebral metastases
6	(F, 30)	Small int.	Carcinoid	+	L+N+B	1	<20	SD, 2 mo	–	↘	2	Dead at 39 mo after SLT
7	(F, 41)	Pancreas	Carcinoid	+	B	1	123	SD, 3 mo	NC	NC	2	Lost to follow-up at 4 mo
8	(M, 55)	Small int.	Carcinoid	+	N+P	2	152	SD, 24 mo	NC	↘	5	Lost to follow-up at 25 mo
9	(M, 50)	Pancreas	Islet cell	0	L	2	<20	PD	–	–	2	Lost to follow-up at 3 mo
10	(F, 65)	Unknown	Carcinoid	+	L	2	149	SD, 6 mo	NC	NC	6	Alive at 6 mo
11	(M, 49)	Pancreas	Islet cell	0	L+N	1	<20	SD, 3 mo	–	–	3	Alive at 54 mo—PR with SLT and CR after surgery
12	(F, 46)	Unknown	Carcinoid	0	L	1	76	SD, 8 mo	NC	–	10	Dead at 14 mo
13	(M, 47)	Unknown	Carcinoid	+	L	1	218	SD, 2 mo	↗	NC	2	Stopped due to GI toxicity—alive at 18 mo
14	(M, 66)	Lung	Carcinoid	+	L	1	184	SD, 17 mo	↘	↘	6	Dead at 36 mo
15	(F, 41)	Small int.	Carcinoid	0	L	1	<20	SD, 7 mo	–	–	5	Alive at 96 mo after surgery and chemoembolisation
16	(M, 55)	Lung	Carcinoid	0	L	1	378	PD	–	–	2	Alive at 36 mo after intra-arterial CT
17	(M, 53)	Unknown	Carcinoid	0	L+B	1	77	SD, 8 mo	↗	–	6	Alive at 8 mo
18	(M, 42)	Pancreas	Carcinoid	+	L+N	2	209	SD, 3 mo	↗	↗	3	Dead at 18 mo after chemoembolisation
19	(M, 48)	Lung	Carcinoid	+	L+N+B	1	722	PD	↗	↗	5	Dead at 24 mo after SLT
20	(F, 65)	Lung	Carcinoid	+	L+N	0	431	SD, 5 mo	↘	↘	5	Alive at 42 mo after SLT and chemoembolisation
Pretreated patients												
21	(F, 48)	Small int.	Carcinoid	+	L+N+P	1	257	PD	↗	–	5	Dead at 29 mo after intra-arterial chemotherapy
22	(H, 54)	Unknown	Carcinoid	+	L		118	SD, 6 mo	↘	NC	6	Dead at 28 mo after intra-arterial chemotherapy
23	(F, 68)	Small int.	Carcinoid	+	N+P	2	94	SD, 6 mo	↘	NC	2	Alive at 24 mo Slowly progressive
24	(M, 20)	Unknown	Islet cell	0	N	1	<20	SD, 3 mo	–	–	2	Dead at 6 mo after SLT

L = liver, Lu = Lung, B = bones, N = nodes, P = peritoneum, GI = gastrointestinal, PR = partial response, CR = complete response, SD = stable disease, PD = progressive disease, NC = no change, SLT = second-line treatment (5-FU+streptozotocin), CT = chemotherapy.

* 5-HIAA: urinary excretion: normal = < 20 mg/24 h.

Table 2. Tumour response according to the site of the primary and histology

	Carcinoid tumours			Pancreatic islet cell carcinomas
	Bowel	Lung	Unknown primary	
Response				
Complete	–	–	1	–
Partial > 50 %	–	1	–	1
No change	4	1	5	3
Progression	1	1	1	1
Total	5	3	7	5
Response rate		2/15 : 14 %		1/5 : 20 %

in response rate according to the type of endocrine tumour or the site of the primary (Table 2). In the group of 4 pretreated patients we observed no complete or partial response although 3 patients have been stabilised for 3–29 months.

Biological response was evaluable in 16 patients with urinary 5-HIAA elevation and in 6 of them (37%) we observed a decrease of more than 30% in the 5-HIAA level. A symptomatic improvement and a decrease in carcinoid syndrome was noted in 4 out of 13 patients. In 2 cases, there was a transitory exacerbation of the carcinoid syndrome for a few days during chemotherapy, but it was controlled by somatostatin administrations [7].

Median survival was 27 months (ET) and the 1-year survival 69% (S.D. 11%) for the entire group (Fig. 1). As there were only 5 patients with pancreatic endocrine tumour (islet cell carcinoma) it was not possible to compare their survival to that of the other patients. 2 were lost of follow-up at 3 and 4 months, 2 died at 9 and 18 months and 1 is alive at 54 months.

Toxicity was acceptable but, although no death was caused by chemotherapy, we noted digestive toxicity grade 3 or 4 (WHO) in 7 patients (35%), mucositis grade 3 in 5 (25%), leucopenia grade 3 in 3 patients (15%), and alopecia grade 3 in 16 patients (80%).

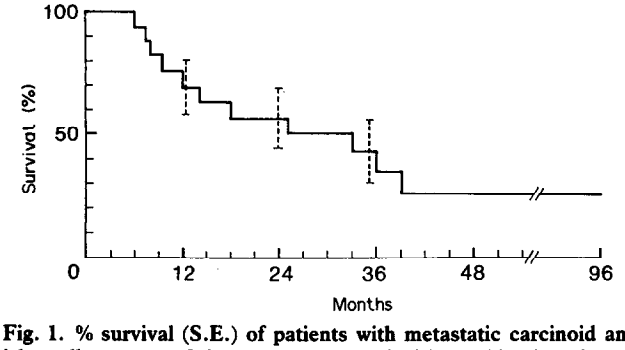

Fig. 1. % survival (S.E.) of patients with metastatic carcinoid and islet cell tumours of the pancreas treated with combination chemotherapy of 5-FU, doxorubicin and cisplatin.

DISCUSSION

In contrast to the general opinion that carcinoid and pancreatic endocrine tumour have good prognoses, our experience confirms that survival is not as good when distant metastases exist. Here, median survival was 27 months. This is consistent with the results of Moertel *et al.* [2], indicating that there is clearly a need for an efficient therapy for these patients.

At this time, standard systemic chemotherapy remains the association of 5-FU and streptozocin; this is not very efficient in carcinoid tumour, with a response rate of 33% (2), but is superior to the administration of streptozotocin alone. We have tried to find a more efficient chemotherapy in combining 5-FU, doxorubicin and cisplatin, but unfortunately observed only a 15% response rate in non-pretreated patients, accompanied by severe gastrointestinal toxicity in 35% of patients. Thus, from this experience, we have not confirmed the encouraging results of Sridhar *et al.* [4] reported on 6 patients with the combination of doxorubicin and cisplatin, and we conclude that the FAP protocol is not an active association in the treatment of metastatic carcinoid tumour. Other chemotherapies must be tested to increase the response rate and survival of patients with metastatic carcinoid and islet cell pancreatic tumours. Interferon alpha (IFN-α) is another alternative to be tested. Beside encouraging trials [8], other studies have not confirmed the efficacy of IFN-α, with tumoral response reported in only 20% [9] and 10% [10] of patients. New trials evaluting the effectiveness of combination of IFN-α and chemotherapy remain, therefore, to be conducted.

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