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Second-line intra-arterial chemotherapy in advanced pancreatic adenocarcinoma

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1. ABSTRACT

The present study was conducted to evaluate activity and toxicity of the FLEC (folinic acid 100 mg/m^2; 5-fluorouracil 1000 mg/m^2; carboplatin 300 mg/m^2; epirubicin 60 mg/m^2) schedule as second-line treatment for progressive locally advanced or metastatic pancreatic cancer (LAMPC). FLEC was administered every 3 weeks with an angiographic catheter introduced into the tumor vascular bed. Thirty-two patients were enrolled. Twenty patients had a PS of 2. Twenty-five patients had metastatic disease to liver. Seven (21.9%) partial responses were observed (WHO criteria). Fifteen patients (46.9%) had stable disease and ten patients (31.2%) had progressive disease. The median OS from the diagnosis was 11.8 months. PS (p=0.0308) and pain (WHO scale, p=0.0222; analogic scale, p=0.0446) significantly improved after therapy. No patient discontinued treatment because of toxicity (NCI-CTC criteria). The current study shows that intraarterial chemotherapy is a good therapeutic option in second-line treatment of LAMPC.

2. INTRODUCTION

Medical treatment of pancreas carcinoma have reached very frustrating results. Surgery remains the mainstay of resectable disease as well as in a palliative setting by ensuring gastrointestinal and biliar transit. Standard first-line treatment of locally advanced or metastatic pancreatic cancer (LAMPC) relies on gemcitabine monochemotherapy which improves clinical benefit and quality of life. Overall response rate of gemcitabine does not reach the widely accepted cut-off (20%) of anti-cancer activity. There is no established second-line treatment for advanced pancreatic cancer after gemcitabine failure. Prognosis is very poor with a median survival of 3-6 months (1). This scenario makes LAMPC the most untreatable disease. The main reason of demise is attributable to the high chemoresistance of the neoplasm. Chemoresistance of pancreatic adenocarcinoma is in part due to the increased expression of the MDR (multi-drug resistant) gene. In addition, two proteins are found in pancreatic neoplasms. 1. The MRP (multi-drug resistance-

associated protein) located on cell membrane where it acts as ATP-dependent membrane pump like P-glycoprotein causing the excretion of cytotoxic agents out of tumour cells (2,3). 2. The LRP protein (lung cancer resistance-associated protein) which is located intracellularly in vaults and transports toxic agents from the nucleus of neoplastic cells to lysosomes (4). One way to circumvent chemoresistance is the administration of high concentration of drugs into the tumor bed. Intraarterial chemotherapy is a procedure used to infuse higher concentrations of chemotherapeutic drugs directly into the artery supplying the vascular bed of a tumour (5). With the intraarterial application, the local concentration at the target site is significantly increased as compared to intravenous infusion. It is further thought that through the first pass effect, systemic effects can be reduced. Previously, Cantore et al showed that intrarterial chemotherapy with the FLEC schedule (Fluorouracil, Folinic Acid, Epirubicin, Carboplatin), is safe and active with a 15% response rate as first-line treatment (6). Second-line treatment of LAMPC remains unexplored. To date no treatment has been shown to be useful in this particular clinical setting. The present study was conducted to evaluate activity and toxicity of the FLEC schedule as second-line treatment for pancreatic adenocarcinoma which progressed after or during first-line chemotherapy.

3. PATIENTS AND METHODS

Patients with progressive LAMPC after or during first line chemotherapy were eligible for this study. Performance status was assessed with the Southwest Oncology Group scale (SWOG). White blood cell count >3000 ml, platelet count >120000, haemoglobin level > 9.5 gr/dl, serum creatinine <1.5 and bilirubin <2.5 times the institutional upper limit of normal were required. No prior radiation therapy was permitted. Before initiation of study treatment, all patients provided written informed consent. Locoregional chemotherapy was administered with an angiographic catheter (Simmons 2; 5 Fr) introduced via the femoral artery into the celiac axis and then into the tumor vascular bed. When liver metastases were present, half of the total dose was infused in the hepatic artery and half according to the primary tumor site. The drugs were diluted in 50 ml of normal saline and were injected over 10 minutes in the following order: folinic acid (FA) 100 mg m2; 5-fluorouracil (5-FU) 1000 mg/m2; carboplatin (CP) 300 mg/m2; epirubicin (EPI) 60 mg/m2. Growth factors (filgrastim) was given at 5mg/Kg/day from day 8 after chemotherapy for five consecutive days.

Treatment was administered every 3 weeks, unless there was insufficient hematologic recovery, in which case treatment was delayed for up to 2 weeks until recovery (neutrophil count $\geq$1,500/μL, platelet count $\geq$100,000/μL). In the event of febrile neutropenia, grade 4 neutropenia lasting more than 5 days, or grade 4 thrombocytopenia, or any nonhematologic grade 3 to 4 toxicity (except grade 3 to 4 elevated AST and ALT) the drugs were reduced of 25%. In the event of grade 3 or higher toxicities, or elevated ALT or AST levels to any grade that did not recover by day 35, the treatment was discontinued.

Computed tomography (CT) scans of measurable lesions were carried out within 4 weeks before the start of the treatment and were repeated every three cycles of intraarterial chemotherapy or at the end of the treatment whenever it occurred first. Responses were to be confirmed by subsequent CT scans 4 to 6 weeks after the initial response documentation. Patients were considered assessable for response if they had a pre and a post-treatment tumor assessment. We planned to administer five cycles of therapy but a further cycle was administered in responder patients. Treatment was stopped for unacceptable toxicity, patient refusal, or investigator decision. In October 2000, the protocol was amended by the introduction of PS3 SWOG patients. CA 19-9 was evaluated at the study entry and at the end of the treatment.

Tumor response was determined using standard bidimensional criteria. The primary study end point was overall response rate (complete response [CR] and partial response [PR]). Disease responses were classified as follows: CR, disappearance of all objective evidence of disease; PR, decrease of 50% or more in sums of the products of diameters of measurable lesions as determined by two tumor measurements; stable disease, decrease of less than 50% or increase of less than 25% in the sums of the products of diameters of measurable lesions; progressive disease, increase of more than 25% in the sums of the products of diameters of measurable lesions or the appearance of new lesions. Toxicities were classified by the National Cancer Institute Common Toxicity Criteria.

The TTP (time-to-progression) was measured from the start of the treatment until progression. OS (overall survival) was measured from the start of the treatment until death resulting from any cause. Patients who were lost at follow-up or who died without documentation of disease progression were considered to have had tumor progression at the time of death, unless there was sufficient documented evidence to conclude that progression did not occur before death. The distribution of time to progression and survival time was estimated using the Kaplan-Meier method.

Weight changes and pain were evaluated before the first treatment and at the end of the treatment (whenever it occurred first). A weight gain of >7% from baseline, substained for more than one month was considered as a positive response. Modification of pain were evaluated using two tools. A subjective numerical pain scale (NPS); the patient himself described the intensity of discomfort in numbers ranging from 0 to 10 (from 0= no pain to 10=maximum pain) and with the WHO scale: grade 0= no therapy required; grade 1=only non-steroidal anti-inflammatory drugs (NSAIDs); grade 2= combinations of NSAIDs $\pm$ antidepressants $\pm$ anticonvulsivants; grade 3= opiate and/or morphine derivatives with or without the previous drugs. Changes of pain degrees were described with descriptive statistics.

Associations between variables related to patient and disease status (pain, weight, performance status,

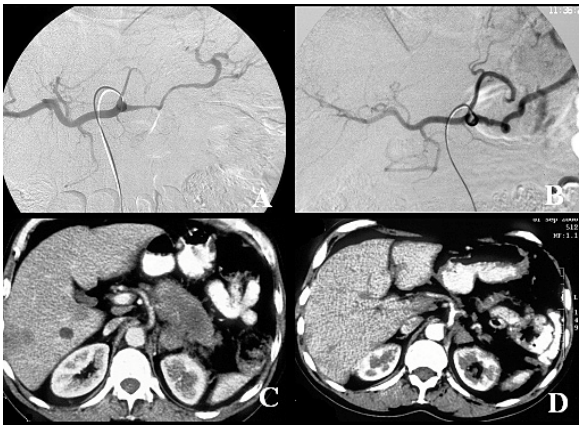

Figure 1. Angiographic study before (A) and after treatment (B). Splenic artery exhibits neoplastic stenosis and dislocation (A) which disappeared after three cycles of intrarterial FLEC (B). Abdomen TC study before (C) and after (D) treatment in the same patient. In C is shown a gross volume mass of the pancreas (body/tail). The patient presents also with hepatic metastases and involvement of the left adrenal gland. After three cycles (D) the pancreatic lesion disappeared and the hepatic metastases showed reduction in number and size. The size of the adrenal gland was stable.

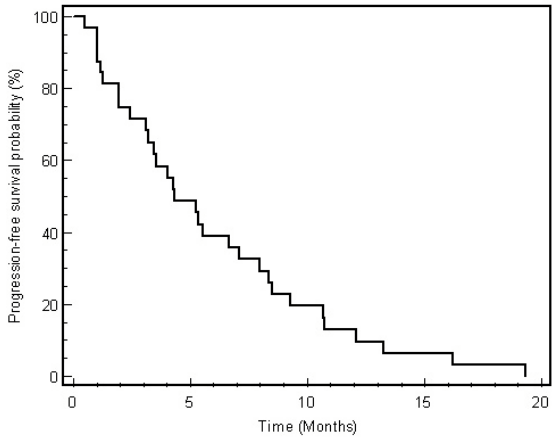

Figure 2. Kaplan-Meier curve of time-to-progression.

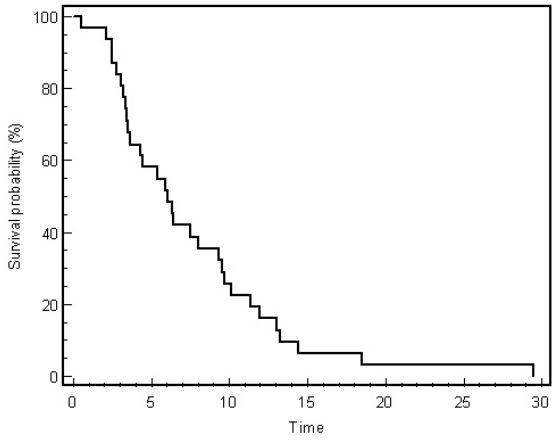

Figure 3. Kaplan-Meier curve of overall survival.

CA19.9) and treatment were studied with the chi-square test. $P<0.05$ were considered statistically significant.

This is a retrospective study based on a consecutive series. The aim was to describe the antitumor activity of FLEC schedule in a population of patients with LAMPC who had experienced progression after or during previous systemic chemotherapy. They were considered inappropriate for further systemic treatments. Chemotherapy offers a response rate of <5-10% in a first-line setting; therefore, a true response rate greater than 20% in a treatment would be considered highly significant.

4. RESULTS

4.1. Patient Characteristics

The characteristics of the patients on the study are listed in Table 1. Between March 1999 and March 2004, 32 patients were enrolled onto the study at the Division of Medical Oncology B of the National Cancer Institute of Naples. The median age at study entry was 62 years (range, 34 to 77 years). There were more men (68%) than women. Sixty-two percent of patients had a performance status of 2 (3 patients had a PS 3). Nineteen patients did not undergo to surgery as primary treatment. Nine patients had received a palliative surgery and 4 patients a surgery with radical intent. All patients presented with progressive disease after first-line chemotherapy. Twenty-five patients had metastatic disease to liver. Prior radiation treatment was not permitted.

4.2. Response

All patients were assessable for the safety analysis and for response. Three patients refused continuation of treatment because of personal aspects after the first cycle. Three patients went off study early, after the first cycle, because of disease progression while on treatment. The overall objective response rates are listed in Table 2. Seven (21.9%) partial responses (PRs) were observed. Fifteen patients (46.9%) had stable disease and ten patients (31.2%) had progressive disease. Responses were observed in patients with liver involvement. Of seven responses, three were observed after three cycles, one after five cycles and three after six cycles of intraarterial chemotherapy. No patients underwent surgery after chemotherapy. For the seven partial responders, the median response duration was 10.6 months (range, 1.6 to 19.3 months). An angiographic and TC study of a responder patient before and after therapy is shown in Figure 1.

4.3. Time-to- progression and survival

All patients were included in the time-to-progression and survival analysis on an intent-to-treat basis (Figure 2 and Figure 3, respctively). Patients who refused the treatment after the first cycle were considered as negative events (progression, death). The median follow-up time was 6.1 months. The median TTP was 4.3 months (95% CI, 2.6 to 7.8 months). The median OS was 6.1 months (95% CI, 3.4 to 9.5 months). The median OS from the diagnosis was 11.8 months (95% CI, 8.6 to 16.0 months) with a six-months survival rate of 85% and 1-year survival rate of 50% of patients (Figure 4). Survival was

Table 1. Characteristics of patients

Characteristic	No. of patients	%
Age, Years		
Median	62	
Range	34-77	
≤65	19	
>65	13	
Sex		
Male	22	68.7
Female	10	31.3
Performance Status (ECOG)		
0/1	9	28.1
2	20	62.5
3	3	9.4
Stage		
Locally advanced (III)	7	21.9
Metastatic (IV)	25	78.1
Liver	25	
Previous treatment		
Palliative intent	9	28.1
Radical intent	4	12.5
No surgery	19	59.4
Chemotherapy		
Gemcitabine	10	31.2
Gemcitabine+Cisplatin	6	18.8
Gemcitabine+Fluorouracil	10	31.2
Two or more	6	18.8
Histology (adenocarcinoma)		
Grading		
2	11	34.4
3	22	65.6
Location of primary tumor		
Head	10	31.2
Body	13	40.6
Tail	4	12.5
Body/Tail	5	15.7

Table 2. Response to treatment

Variable	No.	%
No. of cycles		
Median	3	
Range	1-7	
Type of response		
Complete response	0	-
Partial response	7	21.9
Stable disease	15	46.9
Progressive disease	10	31.2

associated with type of response (median survival for PR: 12.5 months, SD: 6.3 months, PD: 3.0 months, p=0.0001 log-rank test) (Figure 5). Mostly, deaths were related to liver involvement and neoplastic cachessia.

4.4. Performance status and pain assessment

Table 3 shows modifications of weight, SWOG performance status, and pain (analgesic consumption and pain intensity) occurring after intraarterial chemotherapy. Evaluations were performed at the end of the treatment whenever it occurred first. Performance status significantly improved after therapy (p=0.0308). The treatment also significantly improved pain (WHO scale, p=0.0222; analogic scale, p=0.0446). Weight increase >7% was observed in 17/34 (53%) of patients.

4.5. Safety

Patients received a total of 88 cycles. No procedure-related adverse events occurred. The median number of FLEC cycles administered was three (range: one to seven cycles). Only one patient received seven cycles of therapy. Twenty-two (68.7%) patients received three or more cycles of treatment. The major cause of treatment discontinuation was progression of disease. Nine patients (28.1%) required dose reduction because of thrombocytopenia. No patient discontinued treatment because of toxicity. There were no treatment-related deaths. Toxicities observed during the treatment are listed in Table 3. WHO grade 3 and 4 leucopenia, neutropenia, thrombocytopenia, and anemia were observed in 6.2%, 12.5%, 28.1%, and 12.5% of patients, respectively. Transaminases elevation (WHO G3) was observed in one patient (Table 4).

5. DISCUSSION

Patients with LAMPC have limited treatment options and a very poor prognosis. Chemotherapy with or without palliative surgery is the standard of care in such patients (7). However, chemotherapy options are limited and are generally used as palliative treatment. Responses to chemotherapy are typically unsatisfactory (<5-10%). Gemcitabine improves clinical benefit but has no clinical activity in LAMPC. This is mostly due to the high chemoresistance of the neoplasm as well as to its relatively hypovascularization. The locoregional chemotherapy is particularly intriguing because it allows the administration of high concentration of the drugs directly into the tumor vascular bed.

Treatment of progressive pancreatic cancer after first-line chemotherapy is particularly difficult since there are no standard chemotherapeutic options to purpose. Intrarterial chemotherapy has been already shown to be safe and useful in treatment of metastasis from colorectal cancer and other neoplasms (5). The feasibility and efficacy of intraarterial chemotherapy in LAMPC has been already investigated by Cantore et al who found with the same schedule an overall response rate of 15% and an overall median survival of 9.9 months in the first-line setting (6). Pain reduction and weight gain were also observed. In the present study we report in a second-line treatment setting a higher response rate (21.9% vs 15%) than that reported in the first-line setting. Such a different results could be related to the smaller number of our series but also to technical issues. In fact, the study by Cantore et al was conducted in seven different Italian institutions while the present report is a monoistitutional experience. A good expertise with harmonization of the technique is fundamental to appropriately perform and deliver intraarterial chemotherapy. Such issue could be not easily controlled in a multiinstitutional trial. Notably, although we had poor performance status patients in our series we

Table 3. Weight, PS, Pain (WHO and analogic scale), and CA19.9 values before and after treatment

Variable	No. of patients (%)		P
	Before	After	
Weight (Kg)			0.1947
40-60	14 (43.7)	14 (43.7)	
61-70	15 (46.9)	10 (31.2)	
71-80	3 (9.4)	8 (25.1)	
PS (ECOG)			0.0308
0	1 (3.1)	7 (21.8)	
1	8 (25.1)	9 (28.1)	
2	20 (62.5)	10 (31.2)	
3	3 (9.4)	6 (18.8)	
Pain (WHO scale)			0.0222
0	1 (3.1)	8 (25.1)	
1	5 (15.6)	9 (28.1)	
2	15 (46.9)	8 (25.1)	
3	11 (34.4)	7 (21.8)	
Pain (analogic scale)			0.0446
0-5	10 (31.2)	19 (59.4)	
6-10	22 (68.8)	13 (40.6)	
CA19.9			0.1775
0-1500	19 (59.4)	25 (78.2)	
>1500	13 (40.6)	7 (21.8)	

Table 4. Treatment-Related Toxicities Expressed as the Worst Toxicity Per Patient

Type of toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Neutropenia	3	9.4	1	3.1
Thrombocytopenia	5	15.6	4	12.5
Anemia	3	9.4	1	3.1
Mucositis	0	-	0	-
Fatigue	0	-	0	-
Neuropathy	0	-	0	-
Diarrhea	0	-	0	-
Nausea	0	-	0	-
Vomiting	0	-	0	-
Alopecia	0	-	0	-
Hepatic (liver ransaminases)	1	3.1	0	-

Note. Toxicity was assessed using the NCI-CTC scale for toxicity grading.

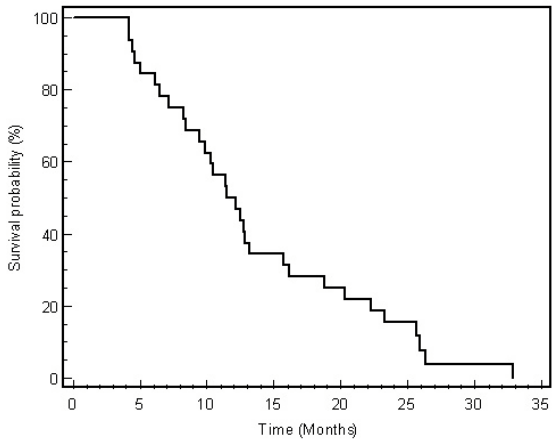

Figure 4. Kaplan-Meier curve of overall survival from diagnosis.

registered no death or complications related to the angiographic procedure.

Very frequently, patients affected by LAMPC experience decrease of performance status and increase of disease-related sympthoms (pain, weight loss, diarrea) so that they became more and more frail. This is the reason for which we also treated patients with SWOG performance status of 2/3. Locoregional chemotherapy allows the administration of cytotoxic drugs directly into the target site where the concentration of drugs is significantly increased as compared to intravenous infusion. Furthermore, through the first pass effect, systemic toxic effects can be reduced. This is particularly desired in such frail patients.

A few prospective studies in second-line chemotherapy of pancreatic cancer have been already conducted mostly with discouraging results. A recent phase II study in metastatic pancreatic adenocarcinoma, who progressed while receiving or within 6 months after discontinuation of palliative first-line chemotherapy with gemcitabine, randomised 38 patients to 3-weekly courses of raltitrexed 3 mg/m^2 on day 1 or irinotecan 200 mg/m^2 on day 1 plus raltitrexed 3 mg/m^2 on day 2. The authors described in the combination arm an objective response rate of 16% with a median OS of 6.5 months and no response in the arm with raltitrexed alone (8). Again, in a pilot study in 17 patients comparing irinotecan alone, or in combination with oxaliplatin and high dose 5-FU/FA only 1 partial response was registered (9). The potential effectiveness of a second- or third-line therapy with weekly paclitaxel after confirmed progression with a gemcitabine-containing schedule for patients remaining in good clinical condition was studied in eighteen patients. Only one patient achieved a complete remission. The median survival time was 17.5 weeks (10). A recent retrospective analysis in thirty-four patients has shown that the G-FLIP regimen is active and tolerable as second-line chemotherapy in a series of consecutively treated patients with metastatic pancreatic cancer. Grade 3-4 thrombocytopenia (53%), and neutropenia (38%) were the most significant toxicities. Based on RECIST criteria a partial response was registered in eight patients (24%). Median overall survival for all 34 patients was 10.3 months (11).

The current study shows that intraarterial chemotherapy is a good therapeutic option in second-line treatment of patients with LAMPC. Responses were systematically evaluate in all patients with a blinded radiology review. The occurrence of objective responses in this clinical setting is very promising and suggests that the intraarterial FLEC schedule has high activity in pancreatic cancer. Improvements in clinical benefit (ie, stable disease, pain and PS improvement, weight gain, decrease in analgesic therapies consumption) were also observed, primarily in patients who responded. The technique is simple and requires in most cases only one day of hospitalization, and can be administered also to patients with SWOG PS 2/3 obtaining sympthoms relief and improvement of performance status. In addition, giving its activity in the second-line treatment of LAMPC, this treatment should be considered in the multimodal treatment

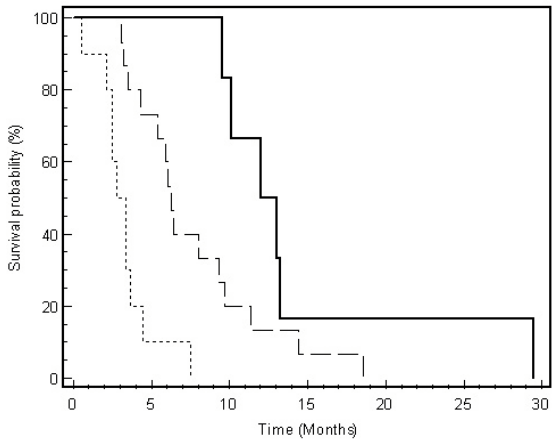

Figure 5. Kaplan-Meier estimate of overall survival by response (PR: partial response, SD: stable disease, PD: progressive disease).

of pancreatic cancer. Although its feasibility only in specialized centers, it should be urgently tested in a large randomized phase III study with the standard first line treatment chemotherapy.

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