Cancer Chemother Pharmacol (2005) 56: 603–609
DOI 10.1007/s00280-005-1012-5

ORIGINAL ARTICLE

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Phase I/II trial of intraperitoneal 5-Fluorouracil with and without intravenous Vasopressin in non-resectable pancreas cancer

Received: 23 November 2004 / Accepted: 3 February 2005 / Published online: 27 July 2005

Abstract *Background*: Systemic palliative treatment with chemotherapy against advanced pancreas cancer has low effectiveness despite considerable toxicity. *Aim*: To investigate the safety, toxicity and tumour response of intraperitoneal 5-Fluorouracil (5-FU) with intravenous Leucovorin and to monitor 5-FU pharmacokinetics in plasma during intraperitoneal instillation with and without vasopressin in patients with non-resectable pancreas cancer. *Patients/methods*: Between 1994 and 2003, 68 patients with non-resectable pancreas cancer TNM stage III and IV, were enrolled to receive intraperitoneal 5-FU instillation 750–1500 mg/m^2 and intravenous Leucovorin 100 mg/m^2 for two days every third week. Tumour response, performance status and toxicity were recorded. Seventeen patients were also treated with intravenous vasopressin 0.1 IU/minute for 180 minutes, during intraperitoneal 5-FU instillation. Area under the curve (AUC) and peak concentration (Cmax) of 5-FU in plasma were analysed. *Results*: The treatment was well tolerated with minor toxicity. One complete response (54.1+ months) and 2 partial responses were observed. Time to progression was 4.4 months (0.8–54.1+), and median survival was 8.0 months (0.8–54.1+). There was a significant reduction of 5-FU Cmax in plasma the second day of treatment if vasopressin was used (3.4 ± 2.5 and 6.1 ± 5.4 μmol/l, respectively, $p < 0.05$). 5-FU AUC in plasma was not significantly affected by vasopressin either day of treatment. *Conclusion*: Intraperitoneal 5-FU is a safe treatment with low toxicity to patients with non-resectable pancreas cancer. Tumour response was 4.4% and median survival time 8.0 months. Addition of vasopressin did not significantly decrease plasma 5-FU AUC but reduced Cmax on day 2 of treatment.

Keywords Intraperitoneal chemotherapy · Pancreas cancer · 5-fluorouracil · Vasopressin · Leucovorin · Pharmacokinetics

Abbreviations 5-FU: 5-Fluorouracil · IP: intraperitoneal · PAC: Port-a-cath · AUC: area under the curve · Cmax: peak plasma concentration · VP: vasopressin

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Introduction

Early detection of pancreas cancer is difficult. Surgical resection offers a chance to cure, but is, due to locally advanced or disseminated disease, possible in only 20 percent of patients [1].

Systemic palliative treatment for advanced pancreas cancer has low effectiveness with 3–4 months prolongation of survival [2–6]. Palliative chemotherapy should be given in selected cases and preferably within clinical trials [7]. New drugs and combinations are being evaluated in larger prospective trials but have so far failed to show a survival advantage.

Intraperitoneal treatment as a route for chemotherapeutic agents to enter microscopic residual disease has been used after surgical debulking in colorectal cancer, ovarian cancer and pseudomyxoma peritoneii. In non-resectable pancreas cancer a debulking procedure is rarely possible. The primary tumour is often adherent to vital vessels and metastases are widespread with numerous lesions in the mesentery, peritoneal surface and liver. Still, there is a rationale to explore the use of intraperitoneal treatment for non-resectable pancreas cancer. Progression of the disease is often by local

lymph node metastases or peritoneal metastases and to prevent the metastatic growth at these locations would be beneficial for the patient.

In a rat model with peritoneal carcinomatosis, uptake of 5-Fluorouracil (5-FU) in tumour was higher when the drug was given intraperitoneally than intravenous [8].With intraperitoneal administration, there is a considerable uptake of 5-FU in the lymphatic vessels and lymph nodes draining the abdominal cavity in pigs[9], high concentrations of 5-FU in the portal and hepatic venous blood [10], and a favourable plasma to peritoneal drug ratio [11]. Intraperitoneal 5-FU is well tolerated [12]. Taken together these observations indicate that the intraperitoneal route is advantageous if we want 5-FU to reach common metastatic sites for pancreas cancer in the peritoneum, lymph nodes and liver.

Even if systemic concentration of 5-FU after intraperitoneal administration is low due to an eighty percent elimination in the first passage through the liver [13], it will lead to dose limiting toxicity. Reduced splanchnic blood flow, as achieved with vasopressin (VP) [14,15], may further enhance the intraabdominal and lymphatic drug exposure, and decrease systemic 5-FU concentration.

The aim of the present study was to investigate the safety, toxicity and tumour response of intraperitoneal 5-FU with intravenous Leucovorin and to monitor 5-FU pharmacokinetics in plasma during intraperitoneal instillation with and without vasopressin in patients with non-resectable pancreas cancer.

Patients and methods

Patients

Two-hundred and twenty-six patients with pancreas cancer were admitted to the department of surgery, Umeå university hospital, between 1994 and 2003. After evaluation with CT scan, magnetic resonance image (MRI) and laparoscopy, 123 patients were intended to a curatively aiming pancreatico-duodenectomy. Eighty-one patients were referred to the department of oncology due to locally advanced or metastatic disease or complicating disease disqualifying from any attempt to do radical surgery (Figure 1). Seventy-seven of these 81 patients were not given systemic therapy but best supportive care.

In total, 68 (29 men/39 women) patients, with a morphologically or cytologically documented non-resectable or metastatic ductal pancreas cancer were included. The patients were required to have a Karnofsky Index [16] of 70 or more and the abdominal cavity should be free of extensive adhesions. Patients were consecutively allocated to the different treament groups, beginning with 5-FU 750 mg/m^2, and with the aim of including 12–18 patients in each group.

Patient baseline characteristics are listed in Table 1. Informed consent was obtained from all patients. The study was approved by the ethical committee at the Medical faculty of Umeå university.

Surgical procedure

A Port-a-cath (PAC, JCL Technic, Vallentuna, Sweden) was applied at laparotomy (n = 51) or laparoscopy (n = 17) in conjunction with primary surgery. The PAC was placed subcutaneously over the right costal edge with the catheter floating free in the abdomen. The intraperitoneal distribution of the instillated drug was controlled by Technetium-99 scintigraphy before starting treatment and then every third month. In two patients the PAC catheter had to be surgically corrected to obtain distribution of the fluid in all four quadrants of the peritoneal cavity.

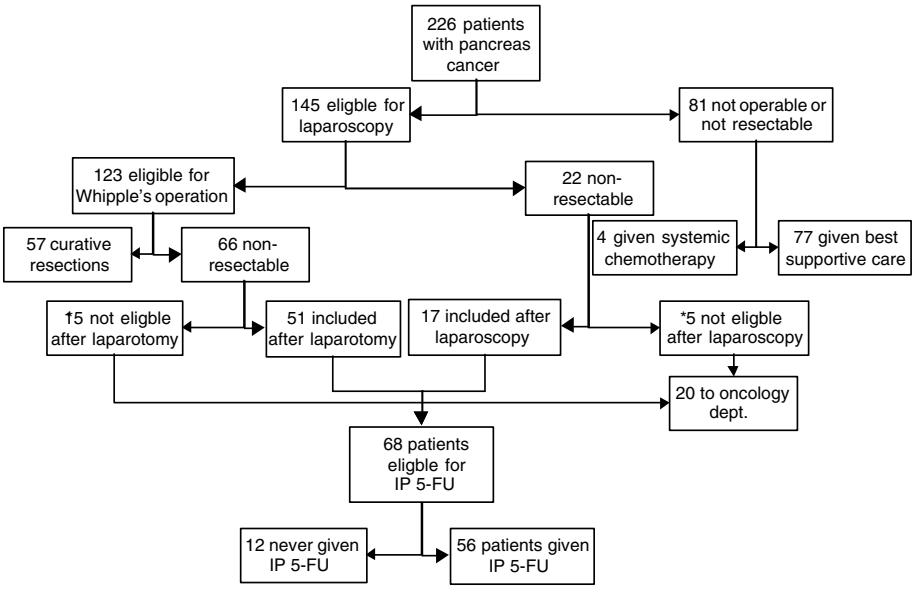

Fig. 1 Patient selection. * Additional renal cell cancer (n = 1), histopathology not conclusive (n = 6), abdominal adhesions (n = 3), referring hospital could not provide treatment (n = 2), choice of the attending surgeon (n = 8)

Table 1 Baseline patient characteristics

	All pts n = 68	0 mg n = 12	750 mg n = 18	1000 mg n = 12	1250 mg n = 12	1500 mg n = 14
Men/Women	29/39	4/8	9/9	4/8	5/7	7/7
Age *	62 (36–89)	65 (53–76)	63 (36–73)	69 (45–89)	57 (47–76)	57 (46–75)
Operation						
Laparotomy	51	7	13	9	12	10
Laparoscopy	17	5	5	3	0	4
Tumour						
Size < 3 cm	14	2	2	2	1	7
Size ≥ 3 cm	41	7	12	5	10	7
NA	13	3	4	5	1	0
Metastases						
Liver	23	5	4	7	2	5
Peritoneum	20	4	6	5	1	4
Differentiation						
High	11	2	5	1	2	1
Intermediate	49	7	13	7	10	12
Low	8	3	0	4	0	1
TNM stage						
III	14	2	1	2	6	3
IV	54	10	17	10	6	11

Legends: Number of patients. *Age (years) given in median (range). NA = not assessable on first Ctscan

Drugs

5-Fluorouracil (5-FU, Flurablastin^R, Pharmacia Sverige AB, Stockholm, Sweden) was prepared in 2000 ml isotonic sodium chloride in intravenous infusion bags. Folic acid (5-formyl-tetrahydrofolate, Leucovorin^R, Wyeth-Lederle, Solna, Sweden) was obtained as an intravenous solution. Vasopressin (lycin-8-vasopressin, Postacton^R, Ferring, Malmö, Sweden) 20 units was diluted in 500 ml of isotonic sodium chloride.

Treatment protocol

The treatment was administered for two consecutive days every third week. The first treatment was given in hospital and the following on an out-patient basis.

5-FU 750–1500 mg/m^2 body surface was administered intraperitoneally by gravity during 30–60 minutes. Thirty minutes after the start of the 5-FU infusion, Leucovorin 100 mg/m^2 body surface was given as a slow intravenous injection. The treatment was repeated the next day. There was no drainage of fluid after treatment. Antiemetics were prophylactically administered. The patients received 5-FU in escalating doses, i.e. the first 18 patients received 750 mg/m^2 5-FU, the next 12 patients 1000 mg/m^2.

Performance status defined as Karnofsky Index, morphine consumption and weight, were recorded at every treatment.

Every third month, tumour response was evaluated with CT scan according to the WHO criteria, clinical assessment and pulmonary X-ray. With signs of progressive disease on CT, clinical tumour progression, intolerable toxicity or withdrawal of patient consent, treatment was discontinued. After discontinuation of the study treatment, patients were given best supportive care or referred to the department of oncology for additional systemic chemotherapy.

Tumour response, safety and performance status evaluations

Tumour response was registered as time to progression and survival time. Time to progression was defined as the time from operation of the PAC to the first objective documentation of tumour progression, or to the time of death in the absence of previous documentation of objective progressive disease. Survival was defined as the time from operation to the date of death.

Safety evaluation parameters included assessment of laboratory values for haematological, renal and hepatic functions every other week, and assessment of adverse advents at every treatment.

Stable performance status was defined as: no worsening of the Karnofsky Index, less than 10% increase in morphine consumption, and a decline in weight of less than 5% from baseline and while in treatment.

5-FU pharmacokinetics

The first seventeen patients, with start immediately before administration of 750 mg/m^2 intraperitoneal 5-FU, were given intravenous vasopressin 0.1 IU/minute during 180 minutes, alternatively day 1 or 2. Blood samples to determine 5-FU plasma concentration were drawn every 30 minutes either from 0 to 180 minutes (432 samples) or from 210 to 390 minutes (82 samples). The samples were centrifuged and frozen until analysis was done by high-pressure liquid chromatography (HPLC) technique [17].

Statistical methods

Values are given in mean ± SD or median (range). Comparison between groups was done with ANOVA. AUC was calculated according to the trapezoidal method with Graph Pad Prism 3.0 (Graph Pad Software Inc., San Diego, CA, USA). Statistica (Statsoft Inc., Tulsa, OK, USA) was used for other calculations. A p-value less than 0.05 was considered significant.

Results

Treatment administration

Of 68 included patients, 56 received at least one two-day intraperitoneal 5-FU treatment. Median duration of therapy was 3.9 months (0.1–29.7). Twelve patients did never start treatment due to rapidly progressive disease (n = 6), patient withdrawal (n = 1) or referring hospital did not commence treatment (n = 5). Two patients in the latter group received systemic chemotherapy.

Treatment was discontinued due to progressive disease on CT scan (n = 23), clinical signs of tumour progression (n = 22), Port-a-cath infection (n = 4), patient withdrawal (n = 4) and incapability of receiving hospital to commence treatment (n = 1). After discontinuation of treatment, patients were submitted to best supportive care (n = 34) or to systemic chemotherapy with gemcitabine or 5-FU/Leucovorin (n = 17 and n = 3, respectively). Two patients are presently in treatment. Six patients given 1000 (n = 1), 1250 (n = 1) and 1500 (n = 4) mg/m^2 intraperitoneal 5-FU are presently alive. During treatment the Karnofsky Index was stable, the weight loss was 6%, and the morphine consumption/24 hrs increased with 100% (from 60 to 120 mg).

No treatment related mortality was observed. Toxicity was low with no WHO Grade 3 and 4 events for doses up to 1250 mg/m^2. In the group given 1500 mg/m^2, three patients experienced angina pectoris. When vasopressin was given, all 17 patients had WHO Grade 1 gastrointestinal toxicity with nausea/vomiting and two patients had diarrhea (Table 2).

Fifteen patients underwent laparotomy during the treatment period. Three patients presented with signs of bowel obstruction and twelve patients with duodenal compression that required a gastric bypass. In five patients moderate adhesions were found. Two patients with biopsy verified peritoneal metastases found at the primary operation, were operated after 2.1 and 3.3 months of intraperitoneal 5-FU treatment, and they had no macroscopic peritoneal metastases at the second operation. One patient re-operated after 21.9 months of treatment, had developed peritoneal metastases.

Time to progression was 4.4 months (0.8–54.1 +), and median survival was 8.0 months (0.8–54.1 +). Time to progression and median survival for patients who actually received treatment (n = 56) was 5.4 months (0.8–54.1 +) and 9.6 months (0.8–54.1 +), respectively. One-year survival for these patients was 32%.

The median survival for patients with liver metastases (n = 23) was 6.3 months (1.0–38.7), and in patients without liver metastases (n = 45) 9.6 months (0.8–54.1 +). The difference between these two groups was significant ($p < 0.038$).

Patients with peritoneal metastases did not have significantly reduced median survival time compared to those without peritoneal metastases, 7.4 months (0.8–54.1 +) and 9.1 months (0.8–40.1), respectively. One patient has an ongoing complete response (CR) (54.1 + months) and 2 patients experienced partial response (PR). Thirty patients achieved tumour control (CR + PR + SD) at three months (Table 3).

When intravenous vasopressin was given day 1 or 2, 5-FU plasma Cmax was 2.34 ± 1.52 and 3.46 ± 2.46 μmol/l at 150 minutes, and AUC was 70 ± 44 and 118 ± 69 μmol/l × hr, respectively. Without intravenous vasopressin day 1 or 2, 5-FU plasma Cmax was 4.25 ± 3.17 and 6.11 ± 5.37 μmol/l at 120 minutes, and AUC was 127 ± 95 and 194 ± 168 μmol/l × hr, respectively. There was a significant reduction of Cmax on day 2 ($p < 0.05$) when intravenous vasopressin was given

Table 2 Adverse advents (WHO) in IP 5-FU for non-resectable pancreas cancer

	750 mg [a] (n = 18)	1000 mg (n = 12)	1250 mg (n = 12)	1500 mg (n = 14)
Gastrointestinal events				
Nausea	17	3	5	7
Emesis	17	2	3	3
Abdominal pain	3	0	3	3
Abdominal tension	0	0	6	10
Diarrhea	2	0	1	2
Hematological events				
Leucopenia	0	0	1	1
Thrombocytopenia	0	0	1	2
Anaemia	0	1	0	3
Miscellaneous events				
Tiredness	1	1	3	1
Angina	0	0	0	3*
Headache	0	0	1	3

Legends: Number of patients that experienced the event once or more. [a] All but one patient were given intravenous vasopressin infusion. * WHO Grade 3 toxicity (all other toxicities were WHO grade 1 or 2)

Table 3 Summary of survival, time to progression, tumour response and secondary chemotherapy

	All pts n = 68	0 mg n = 12	750 mg n = 18	1000 mg n = 12	1250 mg n = 12	1500 mg n = 14
Survival [a]						
All N = 68	8.0 (0.8–54.1)	4.4 (0.8–9.4)	7.6 (0.8–22.1)	8.7 (2.6–54.1)	14.7 (4.4–41.5)	9.1 (1.5–19.7)
+ LM n = 23	6.3 (1.5–38.7)	3.5 (1.5–8.1)	4.8 (2.9–13.1)	7.1 (2.6–38.7)	12.8 (11.9–13.6)	6.5 (1.5–10.5)
− LM n = 45	9.6 (0.8–54.1)	4.6 (0.8–9.4)	8.2 (0.8–22.1)	15.1 (6.2–54.1)	17.9 (4.4–41.5)	11.0 (3.9–19.7)
Time to progression [a]						
All n = 68	4.4 (0.8–54.1)	3.8 (0.8–8.0)	5.5 (2.6–19.6)	3.6 (2.2–54.1)	8.2 (2.8–21.6)	4.1 (2.7–14.5)
Tumour response [b]						
SD [c]	27	NA	8	4	8	7
PR	2	NA	1	0	1	0
CR	1	NA	0	1	0	0

Legends: [a] Median months (range). [b] Number of patients. [c] SD = Stable disease evalutated at three months. –LM = no liver metastases; +LM = liver metastases. PR = partial response. CR = complete response. NA = not assessable

(Figure 2 and 3). AUC was lower, but not significantly, when intravenous vasopressin was given.

Discussion

This study shows that intraperitoneal 5-FU treatment in patients with non-resectable pancreas cancer is well tolerated with no WHO grade 3 or 4 toxicity up to 5-FU doses of 1250 mg/m^2. At 5-FU 1500 mg/m^2 three patients had signs of cardiac ischemia on the second day of treatment, and in one patient activity-associated mild chest pain was noted for 3–5 days after treatment. Angina is a known adverse event from 5-FU treatment [18]. No patient had haematological toxicity that required cessation of therapy. The toxicity was considerably lower than encountered in treatment with gemcitabine, where vomiting (10–27%), alopecia (50%), oral ulceration (14%) and leucopenia (14–26%) is more frequent [19–21]. Combinations of gemcitabine and other drugs, i.e. oxaliplatin, tipifarnib and pemetrexed have recently failed to show significant survival benefit but added further toxicity [6,22,4].

Survival times must be interpreted with caution in this study as well as in other studies, but a median survival time in our study of 8.0 months in all patients and 9.6 months for patients who actually received intraperitoneal 5-FU treatment is encouraging. Systemic mono-therapy employing 5-FU/Leucovorin, gemcitabine or combination-therapy of gemcitabine and oxaliplatin were reported to have survival times of 5.7, 4.4 and 9.0 months, respectively [19,21,6].

The CT response rate of of 4.4 percent is low but does not necessarily reflect lack of treatment efficacy. In the group treated with 1250 mg/m^2 5-FU there was no CT verified tumour response but a median survival of 14.7 months. The effectiveness of a treatment for non-resectable pancreas cancer might better be evaluated by the tumour-inhibiting properties preventing fast progressive disease. There are several indications that intraperitoneal 5-FU treatment had anti-neoplastic activity in this study. One patient with biopsy verified peritoneal metastases had a CR and is alive disease-free at 54 months. Secondly, intraperitoneal 5-FU gave regional control of peritoneal metastases. Of 15 patients who underwent a second laparotomy, two patients had complete macroscopic regression of biopsy verified peritoneal carcinomatosis at the time of the second laparotomy. At the time of a second laparotomy, progress with peritoneal carcinomatosis was only found in one patient. Finally, peritoneal carcinomatosis is common in patients with pancreas cancer and normally

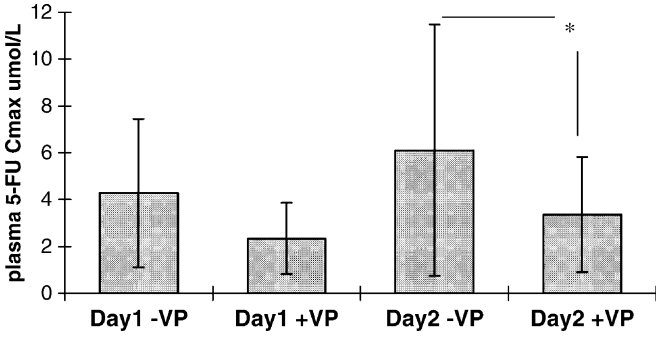

Fig. 2 Cmax of 5-FU (umol/l) in plasma on day 1 and 2 in patients given intraperitoneal 5-FU 750 mg/m^2 without (−VP) and with intravenous vasopressin infusion (+VP). Mean ± SD. *Significant

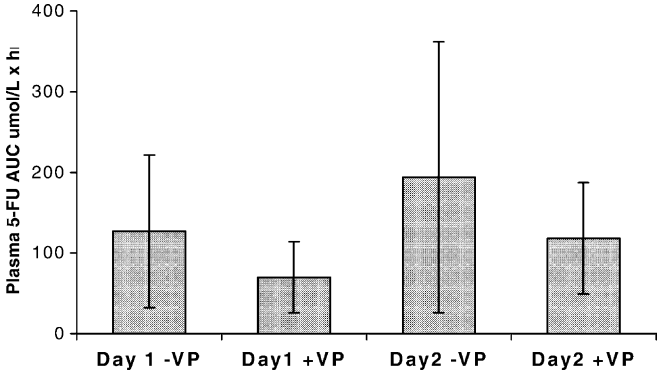

Fig. 3 AUC of 5-FU (umol/l × hrs) in plasma on day 1 and 2 in patients given intraperitoneal 5-FU 750 mg/m^2 without (-VP) and with intravenous vasopressin infusion(+VP). Mean ± SD. *Significant

implies bad prognosis with short survival. In our study patients with peritoneal carcinomatosis did not have significantly worse survival than those without peritoneal carcinomatosis (7.4 vs. 9.1 months).

There is a risk of patient selection bias in this study. Patients considered for surgery initially were judged to have a good performance status, the accrural period was long and it was a phase II study with lack of randomization. Still, patient characteristics in our study do not suggest that patient selection bias was different from other treatment studies. Patients with advanced pancreas cancer present with liver or peritoneal metastases in 23–40% and 25–35%, respectively [23]. In our study, liver or peritoneal metastases were found in 33% and 29%. Patients with liver metastases had in our study significantly reduced median survival, whereas patients with peritoneal metastases had not. Six out of 68 patients in our study did not receive treatment due to rapid disease progression. Of the 81 patients who were not enrolled in this study only 4 patients were given systemic treatment. Another 16 patients failed surgery and did not meet the inclusion criteria for the study. The patients receiving systemic chemotherapy (n = 20) had a median survival of 4.3 (0.8–8.9) months. The 77 patients given best supportive care were supposedly representing a group of patients that would not have been included in other studies and their median survival was only 3.8 (0.6–21.8) months.

The intraperitoneal route offers pharmacokinetic advantages but there are some limitations to be considered. Adhesions after surgery and insufficient instillation volume lead to inadequate drug distribution over the peritoneal surface. In our study the excellent distribution of Technetium-99 in almost all patients verified that adhesions were not a problem. Even in patients with adhesions an uptake of 5-FU via the lymphatics and into the systemic blood circulation occur from non-adhesion areas. With small volumes, that do not fill the abdominal compartment, there is no free movement of drugs. We chose to install a volume of 2000 ml which is necessary to obtain an optimal drug distribution [24]. The mild abdominal pain and discomfort observed in our study were related partly to the distension effect of the fluid, but it could also be due to serositis caused by increasing concentration of 5-FU [25]. In future studies were higher concentrations of 5-FU will be administered an intraperitoneal volume of 1000 ml/m^2 might avoid pain due to distension and still secure optimal distribution. The abdominal discomfort together with added nausea and diarrhea that we observed when vasopressin was given was more troublesome. We believe it was due to the general contractile effect on smooth muscle with increased peristaltic activity. As the pharmacokinetic advantage of vasopressin concerning Cmax and AUC was limited, we did not pursue with vasopressin as the 5-FU dose was increased.

Plasma 5-FU Cmax occurred at 120 minutes without vasopressin and at 150 minutes with vasopressin after the start of the 5-FU instillation. There was a decrease of Cmax when adding vasopressin, and the decrease was significant on day 2 of treatment. Vasopressin had no significant effect on AUC either day. After 180 minutes, the 5-FU concentration in plasma increased markedly (Figure 4). This may be explained by redistribution within the intraabdominal compartment, as patients were permitted to move freely after treatment.

Peritoneal fluid 5-FU concentration after intraperitoneal administration, decreased in a first-order elimination with a half-life of 1.6 hours and after 4 hours 82 percent of the drug was absorbed [26]. In our study we found measurable plasma 5-FU concentrations during at least 390 minutes but not at 24 hours. The magnitude of 5-FU plasma concentrations after 750–1500 mg/m^2 intraperitoneal 5-FU (1500 mg/m^2 data not shown) were in the range of what has been reported by continuous IV 5-FU infusions [27] and the intraperitoneal route therefore offers not only high local 5-FU concentrations but also systemic concentrations with possible antineoplastic activity. Still, the systemic efficacy has to be enhanced, illustrated in this study, by the fact that there were no objective responses of liver metastases and patients with liver metastases did worse than those without liver metastases. In future studies, higher doses of 5-FU could be evaluated for tumour response and for 5-FU pharmacokinetics in plasma and tumour tissue. Intraperitoneal 5-FU in combination with platinum-based chemotherapeutic agents which also have low local toxicity, could be an alternative treatment option.

Patients with non-resectable pancreas cancer do often present with symptomatic disease and until we have substantially better treatment options, intraperitoneal 5-FU offers an active treatment with very little toxicity. Our data from this phase I/II study should be validated in a randomised phase III study where intraperitoneal 5-FU 1250 mg/m^2 will be compared to IV gemcitabine regarding survival and quality of life.

In conclusion intraperitoneal treatment with 5-FU 750–1500 mg/m^2 and intravenous Leucovorin was feasible for patients with non-resectable pancreas cancer. Toxicity was low. Addition of vasopressin did not

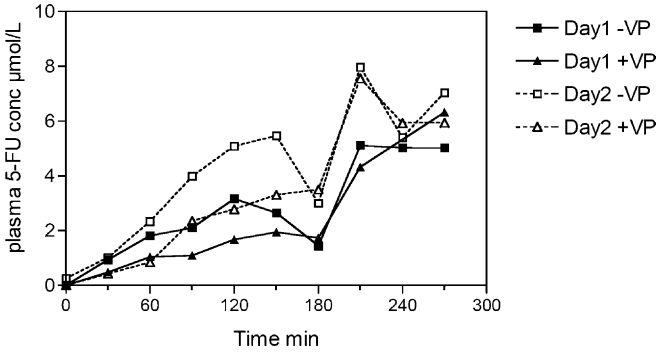

Fig. 4 Mean of plasma 5-FU concentration in patients given intraperitoneal 5-FU 750 mg/m^2 day 1 and 2 with (+VP) and without (-VP) intravenous vasopressin infusion 0-270 minutes after start of intraperitoneal instillation of 5-FU

significantly reduce plasma AUC but added discomfort. The intraperitoneal 5-FU protocol is a safe but not very effective treatment. As long as more toxic systemic treatments fail to be more effective, intraperitoneal 5-FU treatment is an alternative to patients with symptomatic disease where relief of symptoms and stabilisation of tumour growth is acceptable palliation.

Acknowledgements Grant Support: This investigation was supported by grants from Swedish Cancer Society 4144-B99-02XBC, 0512-B99-12XCC, and 4600-B03-03XAC, and the Cancer Research Foundation in Umeå, AMP 97-132 and AMP 99-224

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