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Review

Hyperthermic intraperitoneal gemcitabine chemotherapy for patients with resected pancreatic cancer: Clinical and pharmacologic data

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ABSTRACT

Worldwide, the surgical management of pancreas cancer using the Whipple procedure rarely results in long-term survival even though there is an R0 resection. This manuscript explores the use of hyperthermic intraperitoneal chemotherapy in the operating room to reduce local-regional progressive disease. Gemcitabine monotherapy administered in the operating room as hyperthermic intraperitoneal chemotherapy (HIPEC) is supported by pharmacologic data. The exposure as measured pharmacologically by the area under the curve (AUC) of intraperitoneal concentration times time, divided by plasma concentration times time is 200-500. Data suggests that improved local control with HIPEC with gemcitabine may facilitate an improvement in pancreas cancer treatment that leads the way to more successful strategies with systemic chemotherapy.

KEYWORDS: cancer pharmacology, gemcitabine, chemoradiation therapy, gemcitabine monotherapy, hepatic metastases, hyperthermia, intraperitoneal chemotherapy, local recurrence, local-regional recurrent disease, pancreas cancer, pharmacokinetics

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ABBREVIATIONS

GITSG, Gastrointestinal Study Group; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; PBMC, peripheral blood mononuclear cell; AUC, area under the curve; GOG, Gynecologic Oncology Group; ECOG, Eastern Cooperative Oncology Group; GERCOR, French Multidisciplinary Clinical Research Group; GISCAD, Italian Group for the Study of Gastrointestinal Tract Cancer; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; HIPEC, hyperthermic intraperitoneal chemotherapy.

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer related deaths in the United States of America with an estimate of 34,000 deaths per year [1]. Surgery represents the only definitive treatment option and R0 resection is associated with small improvements in disease-free and overall survival. Advances in surgical technique, anesthesia and perioperative care in the last two decades have led to a substantial decrease in perioperative mortality and morbidity especially in large volume centers. Unfortunately, a majority of patients present with advanced disease and as a result only 10-20% of patients diagnosed with pancreatic cancer are able to undergo potentially curative surgery [2]. Despite careful work-up for metastatic disease prior to surgery, long-term 5- or 10-year survival is rare, even after potentially

curative R0 resection; the 5-year survival is between 10-25% [3]. After curative resection, disease recurrence has been documented in the local and regional area (50%), on peritoneal surfaces (40-60%) and within the liver as hepatic metastases (50-60%) [4].

2. Rationale for perioperative intraperitoneal gemcitabine chemotherapy

The pathophysiology of surgical treatment failure following the Whipple procedure is well established. As a consequence of the narrow margins of resection, there are a large number of local and regional failures. Tumor dissemination and implantation occurs within the resection site during surgery. Conceptually, this forms the basis for administration of perioperative intraperitoneal chemotherapy. The major advantage of intraperitoneal chemotherapy is the high drug level that can be achieved locally with low systemic exposure [5]. This local-regional chemotherapy exposure occurs before pancreas cancer cells become fixed within scar tissue. Several randomized control trials have established the chemotherapy response of adjuvant systemic gemcitabine after potentially curative resection. However, success of systemic chemotherapy in controlling local disease has a weaker rationale and has never been confirmed in randomized trials. The pharmacokinetics of hyperthermic intraperitoneal chemotherapy (HIPEC) with gemcitabine administered intraoperatively establishes it as an excellent choice for local-regional use.

2.1. Absence of benefit of chemoradiation therapy for resected pancreas cancer

Knowledge that a small chance that surgical resection alone will be curative has led to many studies analyzing the benefits of adjuvant therapy in pancreatic cancer. In 1985 the Gastrointestinal Study Group (GITSG) conducted a 2-arm trial randomizing patients with an R0 pancreas resection into 5-fluorouracil (5-FU) based chemoradiation versus observation [6]. The mean survival in the chemoradiation arm was 20 months compared to 11 months in the surgery alone arm. The 5-year survival was 18% and 8% respectively. The trial was able to recruit only 43 patients in 11 years and had to be prematurely closed due to slow accrual and significant benefit favoring adjuvant chemoradiation.

The European Organization for Research and Treatment of Cancer (EORTC) trial conducted an adequately powered study designed to validate the result of the smaller GITSG trial [7]. Adjuvant therapy was similar except that the GITSG study used maintenance chemotherapy while the EORTC trial did not. In the EORTC trial, 218 patients with pancreatic and ampullary cancer were recruited. Randomization was to the surgery only group or pancreatic resection, with split-course radiotherapy (40 Gy) and concurrent 5-FU as a continuous infusion. After a median follow-up of 11.7 years, there was no difference in overall survival between the 2 arms. The limitations of this study were the lack of maintenance chemotherapy and a questionable statistical design that limited its ability to detect a small benefit for adjuvant chemoradiation.

The European Study Group for Pancreatic Cancer (ESPAC) conducted a 2 x 2 factorial design trial between 1994 and 2000 (ESPAC-1) [8]. In the 2 x 2 factorial design, 145 patients were randomized to the chemoradiotherapy arm, and 144 were randomly assigned to no chemoradiotherapy. Radiation was administered as a split course (total 50 Gy), concurrent with 5-FU. There was no difference in the median survival of 15.5 months in the chemoradiotherapy arm and 16.1 months in the no chemoradiation arm. In the final results of the ESPAC-1 trial, the median survival was 15.9 months in the chemoradiotherapy arm and 17.9 months in the group not assigned to receive chemoradiotherapy ($P = 0.05$) [9]. The estimated 5-year survival was 10% in the chemoradiotherapy arm compared with 20% in those who did not receive chemoradiotherapy ($P = 0.05$).

2.2. Adjuvant systemic gemcitabine chemotherapy for resected pancreatic cancer - randomized control trials show activity of this drug

With both EORTC and the ESPAC-1 studies showing no survival benefit, the evidence to support continued use of adjuvant chemoradiotherapy in pancreatic cancer has been markedly reduced. This led to increased interest in clinical trials using chemotherapy alone. The ESPAC-1 trial studied the benefit of chemotherapy which was a bolus of 5-FU administered intravenously. A total of 289 patients were randomized using the 2 x 2 factorial design and followed for 47 months [8].

The survival with chemotherapy was 20.1 months and without chemotherapy were 15.5. The survival benefit was evident not only with R0 but also with R1 resection.

In contrast to inconsistent data for benefit from chemoradiation therapy, clinical research with adjuvant gemcitabine has shown this drug to be a major advance in the treatment of pancreatic cancer. Gemcitabine is a difluorinated analog of the naturally occurring nucleoside deoxycytidine and has shown significant clinical activity in a variety of solid tumors including pancreatic cancer. A significant study regarding the use of adjuvant gemcitabine is the CONKO-001 (Charité Onkologie) study [10]. This multicenter randomized control trial conducted between July 1998 and December 2004 was designed to test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more. A total of 368 patients with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation or chemotherapy were enrolled into 2 groups. One group of patients received adjuvant chemotherapy with 6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks (n = 179), and the second group was treated by pancreas cancer resection alone (n = 175). Median disease-free survival was 13.4 months in the gemcitabine group and 6.9 months in the control group. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. These authors concluded that treatment with gemcitabine for 6 months after complete resection of pancreas cancer significantly increases median and disease-free survival.

An abstract reporting follow-up in 2008 confirms these benefits [11]. The effect of gemcitabine on disease-free survival was significant in patients with either R0 or R1 resection. In the follow-up analysis gemcitabine did improve the overall survival (gemcitabine 22.8 months vs. control 20.2 months). The most impressive statistic was the delayed development of recurrent disease after complete resection of pancreatic cancer compared with observation alone. This clinical trial strongly supports benefit from the use of gemcitabine as adjuvant systemic chemotherapy in resectable carcinoma of the pancreas.

2.3. Current concepts of pancreas cancer management with chemotherapy after cancer resection

Given the conflicting data concerning the use of chemotherapy and radiotherapy in resected pancreatic cancer, the optimal treatment of patients in this setting remains controversial. In Europe, chemotherapy with gemcitabine alone is generally accepted as standard of care, whereas in the United States, chemoradiation therapy may still be recommended especially with an R1 resection.

Recent success with multi-agent chemotherapy regimen used to treat patients with unresectable pancreas cancer has shown increased survival when compared to single-agent Gemzar. The use of FOLFIRINOX regimen resulted in a median overall survival of 11.1 months as compared to 6.8 months in the gemcitabine group [12]. Also, the addition of nab-paclitaxel to gemcitabine increased survival from 6.7 to 8.5 months [13]. Clearly these multi-agent chemotherapy regimens are candidates for adjuvant treatment of resected pancreas cancer.

3. Clinical trials of gemcitabine alone or in combination with other drugs in patients with unresectable pancreas cancer

The current available evidence for treatment for pancreatic cancer suggests that gemcitabine-based chemotherapy should be considered a valid treatment option. In the important study reported by Burris and colleagues, 126 chemotherapy-naïve patients with unresectable pancreatic cancer were randomized to receive either intravenous gemcitabine or 5-fluorouracil. The primary endpoint was a composite of pain measurements, weight, and performance status [14]. Patients treated with gemcitabine derived significantly more clinical benefit than those receiving 5-fluorouracil (23.8% vs. 4.8%, respectively; $P = 0.0022$). In addition there was a statistically significant improvement in overall survival (median: 5.65 vs. 4.41 months, respectively) with a 1-year survival rate of 18% in the gemcitabine cohort compared with 2% in patients receiving 5-fluorouracil ($P < 0.002$).

Berlin and colleagues reported an Eastern Cooperative Oncology Group (ECOG) phase 3 trial including 327 patients with advanced carcinoma

of the pancreas [15]. They showed that 5-fluorouracil, administered in conjunction with gemcitabine, did not improve the median survival of patients with advanced pancreatic carcinoma compared with single-agent gemcitabine. The authors concluded that further studies with other combinations of gemcitabine and 5-fluorouracil are not compelling and clinical trial resources should address other combinations and novel agents. Several other chemotherapy agents have been tried in combination with gemcitabine.

Stathopoulos and colleagues reported that irinotecan with gemcitabine did not show any benefit as compared to gemcitabine alone [16].

The combination of gemcitabine with cisplatin and oxaliplatin has been more encouraging. In a German multicenter study, Heinemann *et al.* enrolled 195 patients to receive either gemcitabine alone or in combination with cisplatin [17]. These results supported the efficacy and safety of an every-2-weeks treatment with gemcitabine plus cisplatin. Median overall survival and progression-free survival were more favorable in the combination arm as compared with gemcitabine alone, although the difference did not attain statistical significance. The French Multidisciplinary Clinical Research Group (GERCOR) with the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) intergroup study compared gemcitabine plus oxaliplatin to gemcitabine alone [18]. The pooled analysis of the GERCOR/GISCAD intergroup study and the German multicenter study indicates that the combination of gemcitabine with a platinum analog such as oxaliplatin or cisplatin significantly improves progression-free survival and overall survival as compared to single-agent gemcitabine in advanced pancreatic cancer especially in patients with good performance status [19].

Scheithauer *et al.* studied gemcitabine in combination with capecitabine [20]. A somewhat superior clinical benefit response rate was seen with the drug combination. However, no advantage over single-agent gemcitabine was noted in terms of objective efficacy parameters.

The combination of gemcitabine and mitomycin C was studied by Tuinmann *et al.* in a trial involving 55 patients with advanced pancreatic cancer [21]. These patients were given gemcitabine 800 mg/m^2 intravenously on days 1, 8 and 15, and mitomycin C 8 mg/m^2 intravenously on day 1 every 4 weeks in an outpatient setting. A median of 3 cycles was administered. The most frequent toxicity was thrombocytopenia grade III/IV seen in 54% of patients. The objective response rate was 29%. Eighteen patients had stable disease resulting in an overall tumor growth control of 62%. Time to progression was 4.7 months and median overall survival was 7.25 months. The authors concluded that the combination was well tolerated. Survival was similar to monotherapy with gemcitabine.

A multi-agent chemotherapy regimen used to treat patients with unresectable disease has shown increased survival when compared to single-agent Gemzar. In 342 randomized patients, the FOLFIRINOX regimen resulted in a median overall survival of 11.1 months as compared to 6.8 months in the gemcitabine group. Clearly, this multi-agent chemotherapy regimen becomes a candidate for adjuvant treatment of resected pancreas cancer [12].

More recently, nab-paclitaxel plus gemcitabine has emerged as a viable option for patients with metastatic pancreatic cancer. Von Hoff has led a phase III multicenter international trial comparing nab-paclitaxel plus gemcitabine with gemcitabine alone as the front-line therapy for patients with metastatic pancreatic cancer. The overall survival was observed to be superior in patients receiving nab-paclitaxel/gemcitabine (8.5 vs. 6.7 months; HR 0.72; P = 0.000015). The 1-year and 2-year survival rates were also better in the combination arm (35% vs. 22%, P = 0.0002; 9% vs. 4%, P = 0.021) [13].

4. Gemcitabine pharmacokinetics

Gemcitabine is a prodrug which has little or no cytotoxic effect in the absence of intracellular enzymes. The drug is metabolized within tissue to the active agent, gemcitabine triphosphate. The efficacy of gemcitabine has been correlated with concentrations of gemcitabine triphosphate accumulated in peripheral blood mononuclear cell (PBMC), which in turn is related to plasma concentration. The rate of intracellular accumulation of gemcitabine triphosphate was highest when plasma gemcitabine was about 20 μmol/L [22]. This would be equivalent to 5.3 μg/ml. Beyond

this, there is enzymatic saturation and further increase in plasma concentration does not produce any increase in intracellular gemcitabine triphosphate concentration.

4.1. Intravenous gemcitabine administration as monotherapy

There are two types of intravenous infusion regimens followed for gemcitabine. First is the fixed dose rate regimen: In this regimen generally 1,000 or 1,500 mg/m^2 is infused during 100 or 150 minutes. The dose rate of 10 mg/m^2/min achieves the target plasma concentration of 20 μmol/L.

In contrast for the standard dose therapy, gemcitabine is administered by intravenous infusion of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Much of the controversy about the use of gemcitabine in further clinical trials has concerned the possible superiority of fixed dose rate over the standard dose schedule. It is a known fact that the fixed dose rate infusion achieves better concentrations of gemcitabine triphosphate in PBMCs, but the clinical benefit of this is uncertain [22].

4.2. Intraperitoneal gemcitabine as monotherapy

In laboratory experiments, gemcitabine was shown to be an effective chemotherapy agent for preventing the postoperative occurrence of peritoneal carcinomatosis. Ridwelski and colleagues used a WAG rat model to investigate the effect of intraperitoneal Gemcitabine on the progression of intraperitoneal adenocarcinoma cells. Intraperitoneal Gemcitabine was used at 24 mg/kg simultaneous with the intraperitoneal inoculation of adenocarcinoma cells or at the same dose, 15, 21, and 27 days later. They also used a no-treatment control group. Simultaneous administration of gemcitabine was the most effective and eliminated the progression of peritoneal metastases in all animals. The delayed gemcitabine administration was effective in reducing the extent of disease as compared to the no-treatment controls, but all delayed treatment groups showed some peritoneal metastases [23].

Clinical and laboratory studies do show a theoretical advantage of intraperitoneal versus intravenous gemcitabine for treating local recurrence or peritoneal metastases [24, 25]. Pestieau and colleagues studied the pharmacokinetics of intraperitoneal gemcitabine in a rat model. The area under the curve ratio of intraperitoneal to systemic drug exposure in the rat model was between 12.5 and 26.8 depending on the dose of intraperitoneal gemcitabine. All tissue samples showed an increased drug concentration when administered with intraperitoneal hyperthermia as compared to a normothermic state [24].

Sugarbaker and colleagues provided data on intraperitoneal gemcitabine in humans by taking plasma and peritoneal fluid samples from patients in the operating room. These data showed that HIPEC with gemcitabine administration at 1,000 mg/m^2 in 2 or 3 liters of peritoneal dialysis fluid showed greatly improved local-regional drug exposure. The area under the curve ratio of concentration times time for intraperitoneal to intravenous drug was 200-500. In this pilot study of patients who had resected pancreas cancer treated with intraperitoneal hyperthermic gemcitabine, considerable benefit was suggested by the pharmacologic data [25]. Of course, the translation of the pharmacologic advantage into an improvement in local-regional disease control will require further clinical studies.

In a study involving nine patients with advanced pancreatic malignancy reported by Gamblin *et al*., intraperitoneal chemotherapy was administered using indwelling peritoneal catheters [26]. Intraperitoneal gemcitabine was well tolerated and no significant toxicities were noted. There was rapid decrease in peritoneal gemcitabine concentration due to almost total absorption of the intraperitoneally-administered gemcitabine. Steady plasma concentrations were reached early implying absorption of all intraperitoneally-administered gemcitabine. These findings combined with the fact that gemcitabine has low local toxicity argue well for its use in intraperitoneal chemotherapy.

One possible criticism of the use of intraperitoneal gemcitabine in carcinoma of the ovary was that better plasma concentrations could be achieved by fixed dose rate systemic infusion of gemcitabine than by intraperitoneal administration. In the study

by Sabbatini *et al*. plasma concentrations of intraperitoneal gemcitabine administered were between 0.92-8.2 µmol which was considerably below the threshold for maximum effect (20 µmol) [27]. However, this criticism ignores the high likelihood that intraperitoneal chemotherapy acts by direct uptake of the drug into cancer cells or peritoneal implants. Furthermore, as Gandhi had pointed out, almost all pharmacokinetic studies on gemcitabine have a caveat that the cellular pharmacokinetic data are obtained from a surrogate tissue (circulating peripheral blood mononuclear cells) rather than from the target solid tumor tissue [22]. The gemcitabine drug levels within solid tumor tissue are not known. Also, levels of gemcitabine-activating and -inactivating enzymes within cancerous tissue such as cytidine deaminase, deoxycytidine kinase and nucleotidases are not well defined. It is highly unlikely that fixed dose rate systemic infusion in comparison to intraperitoneal administration would result in greater area under the curves (AUC) and/or peak levels of gemcitabine triphosphate in tumor cells located at the peritoneal surface of the abdomen and pelvis. Gandhi had suggested the need for pharmacologic studies in which tumor tissue is directly available for measurement of gemcitabine triphosphate concentration.

4.3. Rationale for the use of gemcitabine with moderate hyperthermia

Several cancer chemotherapy agents show increased cytotoxicity when administered with heat [28]. *In-vivo* studies from our laboratory showed enhanced cytotoxicity of gemcitabine when it was used with moderate (41.5 °C) hyperthermia. Tumor growth delay time in the tumor bearing foot of a C3H mouse was increased by 19% when the foot was immersed in a water bath at 41.5 °C [29]. In an intraperitoneal gemcitabine model using Sprague Dawley rats, hyperthermia increased the concentration of drug in peritoneal surface tissues [24]. Yasuda and coworkers used radiofrequency hyperthermia administered at peak gemcitabine concentrations in patients with unresectable pancreas cancer. Mean survival in a group treated by hyperthermia alone was 4.1 months, in the group treated by gemcitabine 7.6 months, and in patients receiving gemcitabine plus simultaneous hyperthermia 12.2 months [30].

In some studies, usually *in-vitro* work, the simultaneous use of gemcitabine and heat has been observed to decrease cytotoxicity. Haveman *et al*. suggested this was caused by inhibition of activation of gemcitabine to the triphosphate metabolite [31]. As shown by Adachi *et al*., with the cell culture at 43 °C for 1 hour, maximum gemcitabine-induced cytotoxicity occurred with drug given 24 hours later [32]. In other *in-vivo* studies by van Bree *et al*., hyperthermia was applied 48 hours after gemcitabine administration. Again, this was a profound 43 °C hyperthermia for 1 hour [33].

In patients receiving intraperitoneal hyperthermia gemcitabine, the core body temperature does not exceed 39 °C. There is a steep gradient from 43 °C in the abdominopelvic space to the pre-peritoneal tissues. Hyperthermia-induced inhibition of the prodrug to the active triphosphate metabolite would not occur within target tissues. Perhaps most important in this treatment plan, only simultaneous hyperthermia with chemotherapy administration is possible.

5. Early clinical results of a phase I/II study with hyperthermic intraoperative intraperitoneal gemcitabine

From April 2007 until August 2011, Tentes and coworkers studied 21 patients with resectable pancreatic cancer, without distant metastatic lesions as assessed by routine preoperative staging [34]. The diagnosis was suggested by physical examination, hematological-biochemical examination, tumor markers (CEA, CA 19-9, CA-125), abdominal and thoracic CT or MRI, and bone scanning. No preoperative histological examination was performed. Patients with periampullary tumors were not included in the study. Patients with resectable pancreatic cancer and limited peritoneal metastases for whom complete resection could be possible, were included in the study. Patients with cancer of the head of the pancreas underwent subtotal pancreatoduodenectomy (Whipple procedure). Distal pancreatectomy was used for cancer of the body or the tail of the pancreas. After tumor resection and before the reconstruction of the alimentary tract, hyperthermic intraperitoneal chemotherapy (HIPEC) was performed for 60 min at 42-43 °C with gemcitabine at a dose of

1,000 mg/m^2. HIPEC was administered using the open (Coliseum) technique. The reconstruction of the alimentary tract was performed after the completion of HIPEC. After subtotal pancreatoduodenectomy the reconstruction was always made with an end-to-side pancreatojejunal anastomosis, end-to-side choledochojejunal anastomosis, followed by a Roux-en-Y gastro-intestinal anastomosis with a second jejunal loop. Cytoreductive surgery with standard peritonectomy procedures was used for the treatment of peritoneal metastases whenever they were found. All patients were followed up at 3-month intervals with physical examination, hematological, and biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), and thoracic and abdominal CT. Recurrences and the sites of recurrence were recorded.

The mean age of the patients was 50-86 years. One patient with cancer of the pancreatic tail and extensive peritoneal carcinomatosis underwent distal pancreatectomy and near complete cytoreduction (CC-1) combined with HIPEC. This was defined as R1 surgery because of possible residual tumor < 2.5 mm left on the peritoneal surfaces of the mesentery. All the other patients had resectable tumors and underwent R0 resection of the tumor combined with HIPEC. Seventeen patients with tumor of the head of the pancreas underwent the Whipple procedure. The other four patients (three with cancer of the tail and one with cancer of the body) underwent distal pancreatectomy.

The hospital morbidity rate was 33.3% (7 patients). The recorded complications are listed in Table 1. One patient was reoperated because of postoperative bleeding that was successfully controlled. One patient was reoperated because the choledochojejunal anastomosis failed, but was successfully controlled by T-tube insertion. The other patient with anastomotic leak underwent conservative treatment. The rate of reoperation was 9.5%. Only one patient was recorded with grade II neutropenia that did not require specific treatment. The hospital mortality rate was 9.5% (2 patients). One of them died because of acute respiratory distress syndrome and the other one of sepsis from an unknown site. The mean hospital length of stay was 18 days.

The 5-year survival rate was 23% and the median survival 11 months (Figure 1). Eleven stage III patients received systemic adjuvant chemotherapy with gemcitabine. One of the patients with stage II disease died during the immediate postoperative period. The median disease-free survival time was 5 months. The median follow-up time was 7 months. During follow-up 9 patients (50%) were recorded with recurrence. Three of them were stage II and 6 were stage III. All these patients had liver metastases and no locoregional recurrence was recorded.

Tentes and coworkers conclude that these data taken together suggest that further studies to test gemcitabine in patients with resectable pancreatic cancer are justified. It appears that intraperitoneal

Table 1. Postoperative complications in 21 patients with pancreas cancer resection plus hyperthermic intraoperative intraperitoneal gemcitabine. (Reproduced from Tentes, A. A., Kyziridis, D., Kakolyris, S., Pallas, N., Zorbas, G., Korakianitis, O., Mavroudis, C., Courcoutsakis, N. and Prasopoulos, P. 2012, Gastroenterol. Res. Pract., Volume 2012, Article ID 506571, 5 with permission).

	No. of patients	%
Postoperative bleeding	1	4.3
Anastomotic leak	2	8.7
Acute respiratory distress syndrome	2	8.7
Sepsis	2	8.7
Grade II neutropenia	1	4.3
Mortality	2	8.7

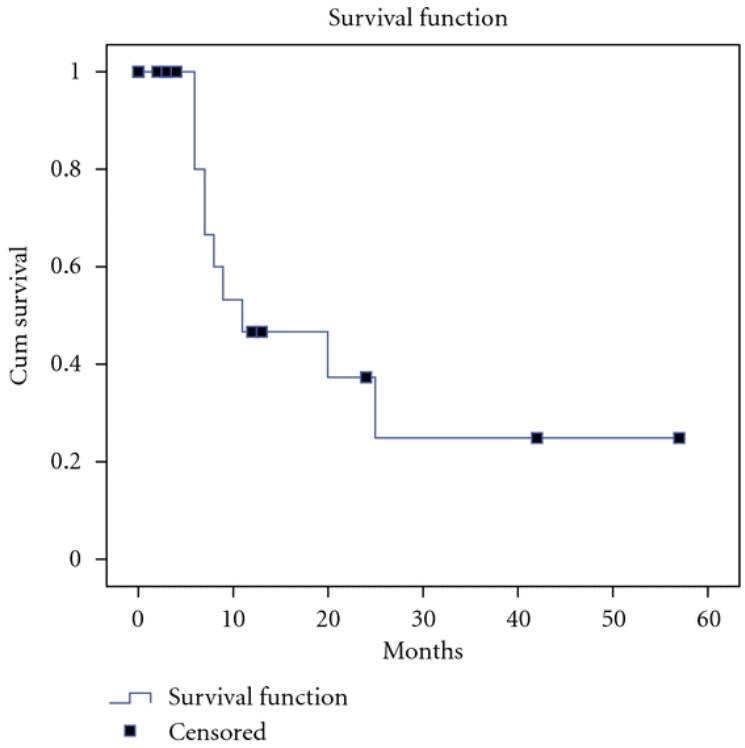

Figure 1. Overall survival of 21 patients with pancreatic cancer treated with complete resection plus hyperthermic intraoperative intraperitoneal gemcitabine chemotherapy at 1,000 mg/m^2. (Reproduced from Tentes, A. A., Kyziridis, D., Kakolyris, S., Pallas, N., Zorbas, G., Korakianitis, O., Mavroudis, C., Courcoutsakis, N. and Prasopoulos, P. 2012, Gastroenterol. Res. Pract., Volume 2012, Article ID 506571, 5 with permission).

chemotherapy may have a favorable effect in eradicating microscopic cancer emboli not only locoregionally but also in the portal venous circulation. It has been found that the measured portal vein concentrations exceeded the measured concentration in other vessels when chemotherapy was administered intraperitoneally [35]. Although the number of patients is small and the median follow-up time short, no patient developed local-regional recurrence. This implies that HIPEC is likely to be effective in eradicating residual microscopic cancer emboli at the resection site and on peritoneal surfaces.

5.1. Pharmacokinetics of hyperthermic intraoperative intraperitoneal gemcitabine

Pharmacologic analysis showed a favorable peritoneal to plasma AUC for gemcitabine ranging from 148 to 368. At the end of 60 minutes, 43-73% of the drug is systemically absorbed. The peak plasma level averages 2.81 mcg/mL [36-38].

The pharmacokinetic information on one patient studied is shown in Figure 2. In this patient, 1700 mg of gemcitabine in 2 liters of 1.5% dextrose was instilled into the open peritoneal space after the pancreatico-duodenal resection was complete. Temperature in the abdomen and pelvis was maintained at 42-43 °C (Figure 3). Uniform distribution of the heat and chemotherapy solution was maintained by manual distribution [39] (Figure 4). The entrance of gemcitabine into tissues was confirmed in that 90% of the total dose of drug was cleared from the chemotherapy solution in 90 minutes. The area under the curve ratio of peritoneal fluid to plasma was 500. At the end of the hyperthermic gemcitabine lavage a single sample of blood from the portal vein showed a concentration approximately the same as systemic plasma concentration. The target tissue was pancreatic cancer cells which may have been disseminated as a result of surgical trauma. Minimal drug was excreted in the urine.

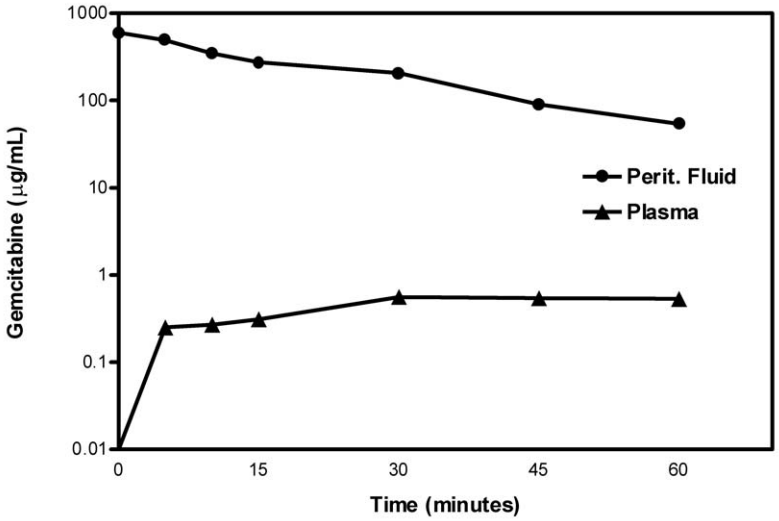

Figure 2. Pharmacology of intraoperative intraperitoneal gemcitabine in a patient with resected pancreas cancer. The drug was used at 1,000 mg/m^2 in 2 liters of 1.5% dextrose peritoneal dialysis solution administered intraperitoneally. The area under the curve ratio of concentration × time intraperitoneal to intravenous was 500. Ninety percent of the drug was cleared from the peritoneal cavity in 90 minutes. Data were taken from the study of a single patient but are similar to those in other patients. (Republished with permission of ALPHAMED PRESS, from Sugarbaker, P. H., Mora, J. T., Carmignani, P., Stuart, O. A. and Yoo, D. 2005, Oncologist, 10, 112).

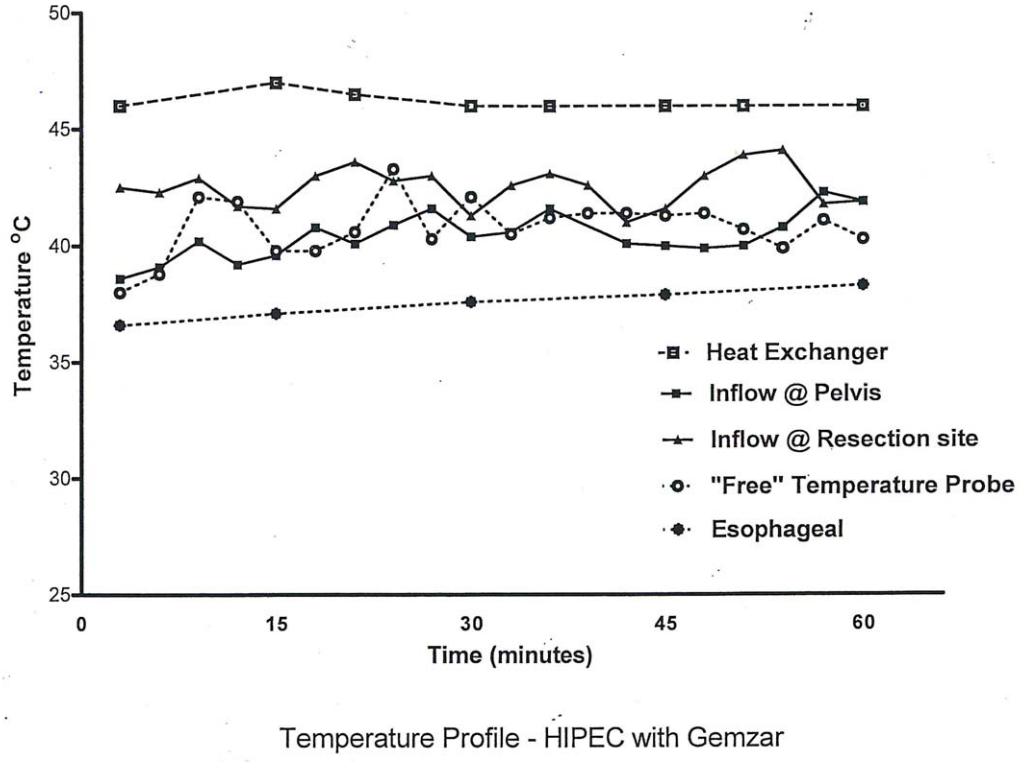

Figure 3. Abdominal and pelvic temperatures maintained for one hour in a patient receiving intraperitoneal gemcitabine.

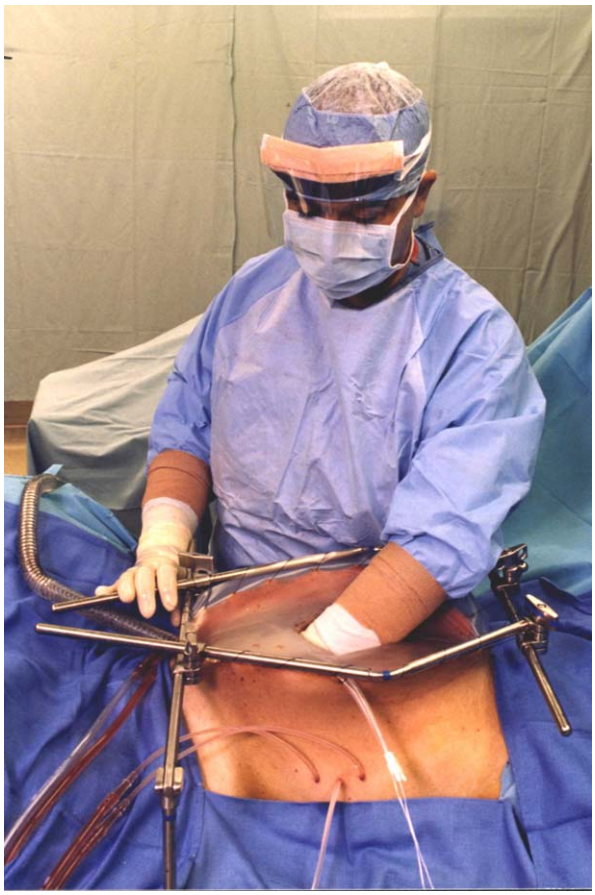

Figure 4. Administration of heated intraoperative intraperitoneal chemotherapy. After placement of tubes, drains and temperature probes, the skin edges are elevated onto the rim of a self-retaining retractor using a running suture. A plastic sheet incorporated into the sutures covers the abdomen and prevents splashing or loss of chemotherapy aerosols into the environment. A slit in the plastic sheet allows the surgeon's hand access to the abdomen and pelvis. His continuing activity guarantees that all abdominal surfaces will have access to uniform doses of heat and chemotherapy. A smoke evacuator pulls the air beneath the plastic cover through a charcoal filter to prevent any aerosols from gaining access to the operating room environment.

5.2. Peak plasma concentration after intravenous administration compared to peak plasma after intraperitoneal administration

An important consideration in the use of intraperitoneal gemcitabine is the concentrations of the drug that are developed by the body compartment. It has been established that 20 µmol/L of gemcitabine in peripheral blood cells correlates with an optimal response. This is equivalent to 5.3 µg/ml. The levels of systemic gemcitabine do not reach 5.3 µg/ml but are very close to this recommended peak plasma level. One must remember that the plasma levels in our patients with pancreas cancer are continued over a one hour time period. The area under the curve of plasma gemcitabine is shown in Figure 2. Although a direct comparison of area under the curve from intravenous administration as compared to the area under the curve for plasma in the administration is difficult, our previous data comparing the area under the curve of plasma exposure by intravenous or intraperitoneal administration are very similar [40].

6. Conclusion

In summary, this manuscript develops a hypothesis suggesting benefit for the use of HIPEC with gemcitabine in the management of pancreas cancer resected by a Whipple procedure. The data taken together provides a rationale for improved local control in patients with resected pancreas cancer. Answers to both pharmacologic and clinical questions can be expected by further studies with gemcitabine using an intraperitoneal route of administration. The preliminary analysis of early data from our study shows acceptable morbidity following hyperthermic intraoperative intraperitoneal gemcitabine. The pharmacologic analysis confirms a high peritoneal to plasma AUC ratio for gemcitabine exposing the surfaces at risk for recurrence to high levels of gemcitabine. Continued treatment and follow-up with analysis of 2-year survival outcomes will be done. Possible addition of other perioperative intraperitoneal drugs is contemplated.

CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest.

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