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Journal

Investigational New Drugs, 33(1)

ISSN

0167-6997

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Publication Date

2015-02-01

DOI

10.1007/s10637-014-0157-7

Peer reviewed

HHS Public Access

Author manuscript

Invest New Drugs. Author manuscript; available in PMC 2017 August 03.

Published in final edited form as:

Invest New Drugs. 2015 February ; 33(1): 109–118. doi:10.1007/s10637-014-0157-7.

Duodenal ischemia and upper GI bleeding are dose-limiting toxicities of 24-hour continuous intra-arterial pancreatic perfusion of gemcitabine following vascular isolation of the pancreatic head: early results from the Regional Chemotherapy in Locally Advanced Pancreatic Cancer (RECLAP) study

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Abstract

Background—Regional chemotherapy is used successfully in the treatment of both primary and secondary malignancies, in particular of the peritoneal surface and the liver, and is currently explored as an attractive approach for patients with locally advanced pancreatic ductal adenocarcinoma. To establish the feasibility and toxicity of regional intra-arterial gemcitabine delivered as a 24-hour continuous infusion to the pancreas as a novel treatment option for patients with locally advanced PDAC a phase I clinical trial was conducted.

Methods—Between April 2011 and September 2013 six patients with biopsy confirmed, borderline or unresectable pancreatic adenocarcinoma, and having received at least one line of systemic chemotherapy, underwent vascular redistribution of the inflow to the head of the pancreas by arterial coil embolization followed by perfusion catheter placement within the splenic artery. Patients were treated with increasing doses of gemcitabine administered by continuous splenic arterial infusion over 24 hours with inter-patient and intra-patient dose escalation scheme. The primary endpoint was toxicity of the intra-arterial gemcitabine regimen and to establish the maximum tolerated dose.

Results—Catheter placement and gemcitabine infusion was successful in all patients enrolled to date (n=6). Four out of 6 patients experienced catheter tip migration requiring replacement or revision. Patients received a median of 4 doses of 24-hour gemcitabine infusion. Two patients developed grade 3 and 4 duodenal ischemia and upper gastrointestinal bleeding. Median overall survival was 15.3 months and median time to progression was 3 months. Three patients (50%,

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Disclosures: None

Conflict of Interests: The authors declare that they have no conflict of interest.

n=3/6) progressed systemically. Two patients had stable disease >4 months following treatment and underwent pancreaticoduodenectomy.

Conclusions—While technically feasible to treat locally advanced pancreatic ductal adenocarcinoma, prolonged regional pancreatic perfusion with gemcitabine following pancreatic arterial redistribution carries a high risk for gastrointestinal toxicity. Shorter infusion schedules with frequent on treatment evaluations should be considered for future clinical trials.

Keywords

pancreatic cancer; gemcitabine; fixed dose rate; regional intra-arterial chemotherapy; regional pancreatic perfusion; duodenal ischemia

Introduction

Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related death in the United States and carries a poor prognosis with an overall survival of 5% [1,2]. In addition to its inherent aggressive biology, PDAC is difficult to diagnose in its early stages due to its anatomical location. Eighty-percent of patients present with metastatic or locally advanced disease, precluding surgical resection, the treatment modality most frequently associated with longer term survival [3,4,2]. Thus, for patients with borderline and locally advanced disease perioperative chemotherapy, frequently combined with radiation therapy, has become a new standard of care in order to (1) select patients with a favorable biology for surgery and (2) downstage tumors to improve the R0 resection rate [5]. However, the unique cytoarchitecture and microenvironment of PDAC represent a significant obstacle to optimizing the impact of cytotoxic therapies in patients with advanced disease. Characterized by desmoplasia and hypoxia, the tumor microenvironment impedes both effective drug delivery and antitumor effect [6]. As a result, only a minority of patients are effectively down-staged and subsequently resected following neoadjuvant chemo-radiation therapy [7,8].

Regional chemotherapy has been used since the 1950s and serves to increase the drug concentration at the site of disease while avoiding systemic toxicities. Regional chemotherapy is used successfully in the treatment of multiple histologies, in particular cancers involving the peritoneal surface and the liver, and has been explored as a novel approach for patients with locally advanced PDAC. A recent review on the various types of regional pancreatic perfusion including patients both with locally advanced and metastatic disease demonstrated a response rate of 58.1% in patients treated with regional intra-arterial chemotherapy (RIAC) compared to 29.4% of patients treated with systemic chemotherapy [9]. In one of the first series on regional chemotherapy following vascular isolation of the pancreatic head for PDAC, Homma et al used either splenic arterial injection chemotherapy (SAIC) or hepatic and splenic arterial injection chemotherapy (HSAIC) of combination 5-fluorouracil (5-Fu) and cisplatinum and reported a response rate of 73.9% and a mean survival of 18.26 months [10]. These outcomes are particularly impressive considering that more than half of patients had concomitant liver metastases at time of treatment. In a more recent study, Aigner et al. confirmed these findings by showing that patients with previously unresectable disease could undergo successful surgery following regional chemotherapy

administration [11]. While these early results confirm the potential promise of pancreas-directed therapy, further progress is currently hampered by the non-standardization of the procedure, including the extent of vascular re-distribution, the value of added procedures like hypoxic abdominal perfusion and chemofiltration, and, in particular, the variations in schedules and types of the delivered cytotoxic agents [9].

Gemcitabine has been shown to improve 1-year survival rates in patients with advanced PDAC [12]. More recently, a randomized phase II trial demonstrated improved median overall survival (8 vs. 5 months, P=0.03) and a more favorable toxicity profile when administered at smaller doses given over a longer period of time compared to the standard dosing regimen [13]. Given the improvement in tumor responses observed with a prolonged rate of gemcitabine administration compared to the standard regimen, and those observed following regional intra-arterial chemotherapy administration, the aim of the RECLAP study was to exploit both strategies to further increase the therapeutic window and maximize anti-tumor efficacy in patients afflicted by locally advanced PDAC. Herein we present the outcomes of the first six patients enrolled on this 24-hour low-dose gemcitabine regional infusion trial and describe two dose-limiting toxicities (DLTs) of duodenal ischemia and bleeding. While three patients had stable disease for a median of 4.7 months, the early significant dose limiting toxicities led the investigators to halt the trial.

Materials and Methods

The Regional Chemotherapy in Locally Advanced Pancreatic Cancer (RECLAP) trial is a single center, phase I trial with three-plus-three inter-patient and intra-patient dose escalation scheme in which cohorts of patients were treated with increasing doses of low-dose gemcitabine administered as a continuous arterial infusion into the splenic artery following pancreatic vascular redistribution over 24 hours. The RECLAP study was conducted from April 2011 to September 2013 after having received full approval by the Institutional Review Board (IRB) of the National Cancer Institute, National Institutes of Health, Bethesda, MD and was conducted at Clinical Center of the NIH by the Surgery Branch, NCI in Bethesda, Maryland, USA. Trial design has been reported in detail previously [14].

The primary endpoint was to evaluate the safety and toxicity of intra-arterial gemcitabine therapy given at low dose in a prolonged infusion over 24 hours and to establish the maximum tolerated dose. Secondary objectives included an evaluation of the overall response rate using RECIST criteria, to determine progression free and overall survival, determine the conversion rate from unresectable to resectable pancreatic cancer, and elucidate potential selection criteria to be used in future studies for patients who present with unresectable locally-advanced pancreatic cancer[14].

Patient Population

Inclusion criteria included 18 years of age or older, histologically or cytologically confirmed, unresectable or borderline resectable pancreatic adenocarcinoma, and no prior history of malignancy within two years prior to enrollment. Patients were included regardless of previous treatment with chemotherapy or radiation therapy. Other inclusion criteria were a life expectancy of greater than 3 months, an Eastern Cooperative Oncology

Group (ECOG) performance status score of 2 or less, and adequate bone marrow (ANCA greater than 1300 per cubic millimeter, hemoglobin greater than 8.0 g/dl, and platelet count, >75,000 per cubic millimeter), liver function (ALT/AST less than or equal to 3 times the upper limit of normal, bilirubin <2 times the upper limit of the normal range, prothrombin time within 2 seconds of the upper limit of normal or INR less than or equal to 1.8), and renal function (serum creatinine less than or equal to 1.8mg/dl).

Arterial redistribution

The strategy for modification of the arterial circulation of the pancreas was adopted from Homma et al (2000) and later refined by Shamseddine et al [15]. Selective embolization of pancreaticoduodenal branches arising from the gastroduodenal and superior mesenteric arteries was performed, resulting in exclusive and complete arterial supply to the pancreas from branches of the splenic artery like the caudal pancreatic artery or the greater pancreatic artery. Unlike the Homma et al procedure, the dorsal pancreatic artery was not embolized, and instead the infusion catheter was positioned proximally into the splenic artery to permit delivery of the chemotherapy to the dorsal pancreatic, great pancreatic, and/or caudal pancreatic arteries. All initial angiographic and infusion port placement procedures were performed under general anesthesia in the interventional radiology (IR) suite. Patients were placed supine and prepped and draped from the neck to the mid-thighs. The right or left femoral artery was catheterized using ultrasound-guided single wall puncture technique and initial celiac and mesenteric angiograms were performed using Cobra or Simmons I catheters without the use of arterial sheaths. A combination of the Progreat microcatheter and Transcend guidewire was employed for super-selective embolization of gastroduodenal and pancreatoduodenal branches with Tornado microcoils (Figures 1A–G). Cone-beam CT scans were performed following contrast injection via the perfusion microcatheter to determine relative contribution to pancreatic versus duodenal blood supply in an attempt to avoid embolization of vessels which appeared to supply duodenum only. Although the possibility to embolize the inferior pancreatic duodenal arcade by retrograde catheterization via the gastroduodenal artery was specifically examined, direct antegrade embolization was most often performed from superior mesenteric artery access. Post-embolization arteriography confirmed target vessel occlusion, while arterial phase cone beam CT images of the pancreas were obtained following splenic artery catheterization in an attempt to confirm pancreatic glandular enhancement and successful vascular redistribution (Figure 2A).

Placement of arterial infusion catheter

Two approaches were employed for arterial port and infusion catheter placement purposes. Selective catheterization of the splenic artery was accomplished after completion of the arterial embolization procedure, and catheter exchange was performed over a V-18 0.018-inch guide wire for a 5F Anthron infusion catheter mounted on a Progreat microcatheter. A subcutaneous pocket was then created by gentle blunt dissection in the area of the anterior superior iliac spine. The Anthron catheter was tunneled to the subcutaneous pocket and attached to a Celsite port. The port was then sutured to the abdominal fascia using 2-0 Prolene suture (Figure 2B). When celiac encasement precluded advancement of the Anthron catheter into the splenic artery, celiac access was achieved via left subclavian artery

catheterization. In these instances, a left infraclavicular subcutaneous pocket was created for the Celsite port, and the port was sutured to the claviculopectoral fascia (Figure 2C). Patients were placed on full anticoagulation using low molecular weight heparin following placement of the perfusion catheter.

Confirmation of catheter position and patency

Following port placement, hourly port site visual checks were performed to confirm hemostasis. The port and catheter were flushed with normal saline at a rate of 10cc/hour overnight. The following day the patient was returned to the IR suite and a scout abdominal image was obtained to assess catheter tip position. Contrast was injected and digital subtraction imaging obtained to confirm catheter and port patency and position. If the catheter tip position was confirmed to be in the splenic artery, gemcitabine was started (18 mg/m2/24 hr for cohort-1, 36mg/m2/24hr for cohort-2, 72mg/m2/24hr for cohort-3). The infusion was started in the IR suite and the patient was then transferred to the floor. The infusion was continued for 24 hours. The arterial port was then decannulated, flushed with 10cc of NS and then 1:1,000 units of Heparin corresponding to the combined volume of the Anthron catheter and Celsite port, and the patient was discharged. Seven days later the patient returned for an outpatient examination where the port was again flushed and refilled with NS and 1:1,000 unites of Heparin to correspond with the volume of the catheter.

Chemotherapy

All patients underwent angiographic confirmation of catheter location and laboratory evaluation prior to each course of chemotherapy infusion. Laboratory evaluation included a complete blood count and differential, serum biochemistry, serum amylase and lipase, and renal and hepatic function tests. Treatment commenced following confirmation of infusion catheter tip position in the splenic artery or celiac axis (celiac encasement). The first hour of the first infusion was administered in the Interventional Radiology Department after which the patient was transferred to the floor.

Gemcitabine was administered in 100ml of 0.9% Sodium Chloride over 24 hours via infusion pump every 14 days +/− 3 days (one cycle) as per dose escalation schema. Two cycles constituted one course. The starting dose for the first three patients (cohort 1) was 18 mg/m2/24 hours (10% of the similarly administered 24-hr infusion of gemcitabine IV dose). This dose was selected based on previously published work from Shamseddine et al. indicating a significant reduction in the area under the plasma concentration time curve from 0 to 270 minutes and a decrease in the peak plasma concentration compared to the IV route [15]. At least 3 patients were required to have completed each cohort treatment without grade 3 or higher toxicity.

Dose escalation could proceed after the third patient in each cohort had no DLTs at the day 14 ±2 days toxicity evaluation provided no DLT’s occurred at that dose level. The MTD was defined as the highest dose that induces drug-limiting toxicity in no more than 2 patients among a cohort of 6 patients. Only DLTs that occurred during Cycle 1 of each dose level were used to determine the MTD. Patients were divided into cohorts and began dosing at successively higher doses until MTD was established or up to 165 mg/m2/24 hours. Adverse

events were reported according the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Clinical and Radiological Assessment

At the end of each course (every 8 weeks) patients underwent evaluation for response with a triphasic CT-scan of the chest, abdomen and pelvis with 1mm slice interval, MRI, and FDG PET. Radiographic response was determined by RECIST criteria [16,17]. Secondary endpoints included progression free and overall survival, as well as the conversion rate from unresectable to resectable pancreatic cancer. Time to progression was defined as the time interval from the start of chemotherapy infusion to disease progression defined by RECIST criteria. Resectability was determined as per the ISGPS criteria [18]. Patients deemed resectable must have had chemotherapy discontinued for at least 4 weeks prior to surgery and all toxicities must have resolved to grade 1 or better.

Results

Patient Population

Between April 2011 and September 2013 six patients met the inclusion criteria and were enrolled in the study. Patient demographics are shown in Table 1. The median age was 66.5 years (range 56–71). All patients were Caucasian and a third were men. All patients had an ECOG status of 0 except patient 6 who had an ECOG status of 1. The median time from diagnosis to trial enrollment was 8.5 months (range 5–16). Most patients (83%) had received a single course of the chemotherapy prior to enrollment. Four patients had previously received radiation therapy and a similar number of patients (50%) had undergone surgical exploration. The median serum CA19-9 level at the time of enrollment was 133 units/ml (range <1.0–521.0) and varied amongst patients.

Catheter Placement

Hemodynamic change and placement of the perfusion catheter was successful in all patients (n=6/6). Two out of 6 patients (patients 1 and 3) required a subclavian approach for placement of perfusion catheter due to celiac axis encasement or subsequent catheter tip migration requiring revision. There were no procedure-related mortalities or late sequelae (arterial stenosis or aneurysm). Four of 6 patients required port revision secondary to infusion catheter migration. Patient 3 required three revisions of the port site secondary to port dislocation and catheter replacement secondary to catheter migration.

Safety

A total of 33 cycles of intra-arterial gemcitabine were administered by the dose escalation schema shown in Table 2. The median number of cycles administered per patient was 4 (range 4–9). No toxicities were seen in four patients treated at the 18mg/m2 dose level. Four patients reached the 72mg/m2 dosing of gemcitabine and completed two cycles, two patients received two cycles at the 96mg/m2 dose, and one patient reached a the dose level of 115mg/m2. There were no immediate complications or mortality during regional infusion of gemcitabine. Adverse events are summarized in Table 2.

Four patients developed a grade 3 or higher adverse event related to pancreatic perfusion and regional gemcitabine delivery (67%, n=4/6) and two patients out of 6 (patients 1 and 4) developed dose-limiting toxicities. Both patients presented with melena secondary to upper gastrointestinal bleeding and grade 3–4 anemia that required multiple blood transfusions. Endoscopic evaluation of both patients revealed duodenitis with contact bleeding, friable duodenal mucosa, and signs of ischemia involving segments D1 and D2. In Patient 1 this occurred at the 36mg/m2 dose and presented on day 12 of cycle 4 of gemcitabine administration. Patient 4 developed a less severe, but more protracted course of melena and presented 2 weeks after infusion at the 115mg/m2 dose. Upper endoscopy showed multiple ulcers in D1 and D2 extending into the antrum in the background of duodenal ischemia (Figure 2). Both patients were managed with prolonged intravenous proton pump inhibitor therapy and multiple transfusions and fully recovered without surgical intervention. Due to the precipitous blood loss patient 1 developed Grade 4 anemia. Grade 3 hematologic toxicities occurred in 2 patients as a result of anemia (50%, n=3/6); one of whom was patient 4. Grade 3 nausea occurred in 1 patient (14%, n=1/6). Elevated transaminase levels occurred in one patient (Grade 3). Constitutional symptoms (fatigue, grade 2–3) observed in three patients were more frequently attributed to disease progression. The Data Safety and Monitoring Board (DSMB) reviewed these early toxicities. Study closure occurred June 2014.

Efficacy

Median overall survival was 15.3 months (3–17 months). Median time to progression was 2 months overall (1–22 months). There were no responses by RECIST or EASL criteria. Three patients had stable disease (Patients 1, 2, and 4) for≥ 4 months. The median time to progression in these patients was 4.7 months. Patients 2 and 4 following 8 and 9 cycles respectively of intra-arterial gemcitabine underwent Whipple surgery. Patient 2 had borderline resectable disease when enrolled, stable disease four months after arterial infusion and slight reduction in tumor volume following pancreatic perfusion before being taken to the operating room where an R0 resection was performed (Figure 4). Multiple neo-vessels, in particular off the hepatic as well as splenic artery had developed (Figure 5) requiring ligation during surgery. On final pathology the tumor was a 3.8 × 3 ×2.5 cm pancreatic adenocarcinoma and contained extensive, dense fibrosis and areas of necrosis. Patient 4 was also taken to the operating room following a 4-month period of stable disease. However, on final pathology, the patient was found to have carcinoid. Following infusion a biochemical response by serial CA 19-9 measurements was observed in only one patient treated, 4 out of 6 patients enrolled onto the study had preoperatively elevated CA19-9 levels. The median time to progression for patients with PDAC was 3 months. Three patients recurred systemically, including in the liver or the peritoneum, either while on treatment or shortly thereafter (Table 3).

Discussion

Notorious for its aggressive biology, pancreatic ductal adenocarcinoma (PDAC) is only marginally sensitive to both systemic chemotherapy and radiation therapy. Due to its unique cytoarchitecture and desmoplasia, drug delivery is significantly reduced [7]. As such,

regional chemotherapy is an attractive approach for patients with locally advanced PDAC to enhance drug delivery, increase the therapeutic window, and reduce systemic toxicity.

Previous clinical efforts where regional pancreatic perfusion has proven efficacious have been hampered by the heterogeneity of patients enrolled and the variety of different treatment strategies employed. The study by Homma et al. treated patients with both locally advanced inoperable pancreatic cancer and metastatic disease. Other trials have been conducted using various single or combination regimens of agents, varying treatment schedules, or lacked standardized strategies for successful pancreatic arterial redistribution including lack of angiographic or cross-sectional validation thereof. In order to address some of these limitations the Regional Chemotherapy in Locally Advanced Pancreatic Cancer (RECLAP) trial treated only patients with locally advanced PDAC, used a single, standardized chemotherapy regimen which had previous PK data available, and administered the chemotherapy using a consistent pattern of vascular redistribution directed by a single interventional radiologist. Herein we report the early results of this phase I effort designed to establish the safety of prolonged, low-dose intra-arterial gemcitabine regional pancreatic chemotherapy infusion.

Our pancreatic vascular redistribution strategy was based upon the approach of Homma et al [10]. We opted to omit embolization of the dorsal pancreatic artery and instead place the infusion catheter tip more proximally in the splenic artery to allow chemotherapy infusion into this vessel. This approach likely contributed significantly to the higher observed rate of catheter tip migration in our patients, in contrast to the 13% rate for splenic artery catheters observed by Homma et al. All patients in our study successfully underwent vascular redistribution including embolization of gastroduodenal and inferior pancreaticoduodenal arterial supply. In general, the procedure was tolerated well with acceptable catheter-related morbidity. Unintended branch vessel chemoinfusion was avoided by confirmatory arteriogram immediately prior to the start of infusion. No splenic artery thrombosis or port-related hemorrhage or infection was observed. We employed cone-beam CT imaging to 1) identify proportional supply to the pancreas by vessels targeted for embolization, and 2) confirm opacification of the pancreas via the splenic artery after the embolization procedure. Streak artifact generated by the embolization coils may limit these post-embolization studies, but it was possible to rule out off-target embolization of jejunal or hepatic arterial branches and evaluate pancreatic enhancement following completion of revascularization. Despite sparing branches of the GDA and IPDA that predominantly supplied the duodenum, we observed duodenal toxicity related to the combined embolization and infusion procedures.

The major toxicity in our trial was duodenal ischemia resulting in significant upper gastrointestinal bleeding in two patients. Both patients presented with melena at 5 and 16 days respectively following vascular redistribution and gemcitabine perfusion. Specifically the duodenal hemorrhage did not appear to be related to gemcitabine dose, as it occurred in Patient 1 at a dose 36mg/m2 and in Patient 4 at 115mg/m2. Duodenal ischemia, including ulcer formation and necrosis, are uncommon complications of synchronous GDA and IPDA embolization for non-variceal upper gastrointestinal hemorrhage, thus we believe that the observed complications are specific toxicities related to gemcitabine, and the length of

gemcitabine perfusion [19]. The GI toxicity was also observed despite avoidance of complete isolation of the duodenal arterial supply, and was not reported in the Homma et al study which did not use gemcitabine. Both instances, however, responded to non-operative management following cessation of perfusion.

That prolonged gemcitabine perfusions likely played a causative role in the observed upper GI toxicity is also supported by the specific metabolism of gemcitabine and clinical observations in patients treated with prolonged gemcitabine infusion regimens. High levels of the intracellular gemcitabine metabolite dfdCTP are not only required for tumor response but dfdCTP levels also contributes to toxicity referable to gemcitabine [20,21]. The accumulation of intracellular dfdCTP is the result of multiple factors, including the dosing regimen and patient genetic factors like expression levels of transmembrane nucleoside transporters [22]. Previous studies comparing fixed dose rate (FDR) administration and the standard 30 minute infusion have demonstrated an increase in dfdCTP associated with the prolonged duration of infusion with the FDR approach.

A previous randomized phase II trial on systemically administered gemcitabine has shown improved outcomes when administered at smaller doses given over a longer period of time [13]. Anderson et al. reported on a phase-I study of a 24-hour infusion of gemcitabine in previously untreated patients with inoperable non-small-cell lung cancer and reported a maximum tolerated dose (MTD) of 180mg/m2/24hr, with dose limiting toxicities (DLT) being neutropenia and lethargy [23]. These findings were confirmed by Pollera et al who also demonstrated a relationship between the length of infusion and tumor efficacy of gemcitabine when used to treat patients with non-squamous cell lung cancer. More so, they found that even at the reduced dose of 300mg/m2 gemcitabine had retained antitumor activity when administered as a prolonged infusion, but reduced toxicity compared to the higher dose of 850mg/m2[24]. To this end, in the only study to date to include comparative PK data from intra-arterial and systemic gemcitabine administration for treatment of PDAC, Shamseddine et al reported no grade III or IV toxicities following as much as a 270 minute infusion schedule of intra-arterial gemcitabine[15]. Thus, to determine whether additional prolongation of the infusion period would further increase the therapeutic window and maximize antitumor efficacy we elected to extend the time of perfusion to 24 hours in our study.

A unique gastrointestinal toxicity profile associated with prolonged infusion of gemcitabine has been reported [25,22,24]. As a single agent for relapsed acute myelogenous leukemia, the escalation in duration of gemcitabine infusion was associated with increased nausea and vomiting [26]. More so, the incidence of toxicities (including mucositis and nausea) at infusion durations of less than 15.4 hours and more than 12 hours was significantly different (3/14 vs 3/5, P = 0.04) [26]. In another Phase I trial, when combined with mitoxantrone, prolonged infusion of gemcitabine 10mg/m2/min for 12 hours was used to induce significant responses in patients with refractory acute leukemia[25]. While the regimen achieved plasma concentrations sufficient for maximal intracellular activation, 67% of patients treated for 21 hours developed grade 4 esophagitis and/or stomatitis requiring nutritional support [25]. Severe stomatitis or esophagitis were the most common non-hematologic adverse events and the primary cause of DLT in the study overall. Similar to other reports using

systemic gemcitabine, patients also experienced anemia and nausea [12]. However, the severity of these was higher in our study where a fixed dose rate was used (grade 4 anemia and grade 3 nausea). More so, the observed toxicities in our study were increased compared to those of other trials where regional intra-arterial gemcitabine was administered [15]. While not directly measured in our study, we believe that the combination of hemodynamic changes including relative hypoperfusion and hypoxia together with the prolonged 24-hour infusion may have resulted in a toxic increase of dfdCTP to the duodenal mucosa overwhelming its defense mechanisms to the acid milieu. The study protocol required all patients to take proton pump inhibitors and it is not known if the cessation of the gemcitabine perfusion or conversation to intravenous acid suppression was the critical intervention in order to restore stability and integrity of the duodenal mucosa after the GI bleeding was discovered. The fact that duodenal bleeding and mucosa compromise was discovered at different doses of gemcitabine could be due to variations in genetic differences in gemcitabine phosphorylation by deoxycitidine kinase or transport by human concentrative nucleoside transporters (hCNTs) or due to variations in duodenal involvement of the vascular redistribution intervention [22]

The response rates in our trial were generally poor compared to more recent phase II trials where a different chemotherapeutic agent was used [27,28,10,29]. Hong et al. used intra-arterial infusion of gemcitabine 1,000mg/m2 and 5-fluorouracil 600mg/m2 in 25 patients and reported a response rate of 32% compared to the 23% response rate of the control group treated with the same regimen intravenously[29]. The median survival for the treatment group was 10 months compared to 7.3 months in the control arm. Liu et al. reported a response rate of 54% (n=14/26) and median survival of 21 months in patients treated with superior mesenteric arterial infusion of gemcitabine (100mg/m2) and cisplatin (50mg/m2) compared to 33% (9/27) and 14 months in those treated intravenously [28]. Toxicity in both of these trials was comparable to the intravenous route, but patients did not undergo extensive coil embolization and hemodynamic change prior to infusion. Hence, the degree of hemodynamic change is likely another important contributing factor for the observed toxicities in our study. The degree of hemodynamic stress placed on the tissues was evident in one patient where neovascularization occurred (Figure 4A and B) following revascularization. Obtaining a balance between the improved gemcitabine bioavailability with the selective infusion of gemcitabine at the fixed dose rate and the induced hypoperfusion, relative hypoxia, and associated duodenal toxicity when combining these approaches will be central to further optimizing this drug delivery platform.

In conclusion, the combination of a prolonged 24-hour rate of gemcitabine infusion with the extensive embolization required to achieve vascular redistribution in the pancreatic head led to significant toxicities at early doses, suggesting that the side effects of this approach on the upper gastrointestinal tract are prohibitive for further development of fixed-dose, prolonged gemcitabine perfusions. Additionally, this approach requires an inordinate degree of expertise and resources, and was further limited by rapid systemic disease progression in more than half of the patients. The value of intra-arterial pancreas-directed perfusion following vascular re-distribution may lie in the administration of less toxic chemotherapy infusion regimens, combinations thereof, or of more novel agents with poor systemic bioavailability or instability.

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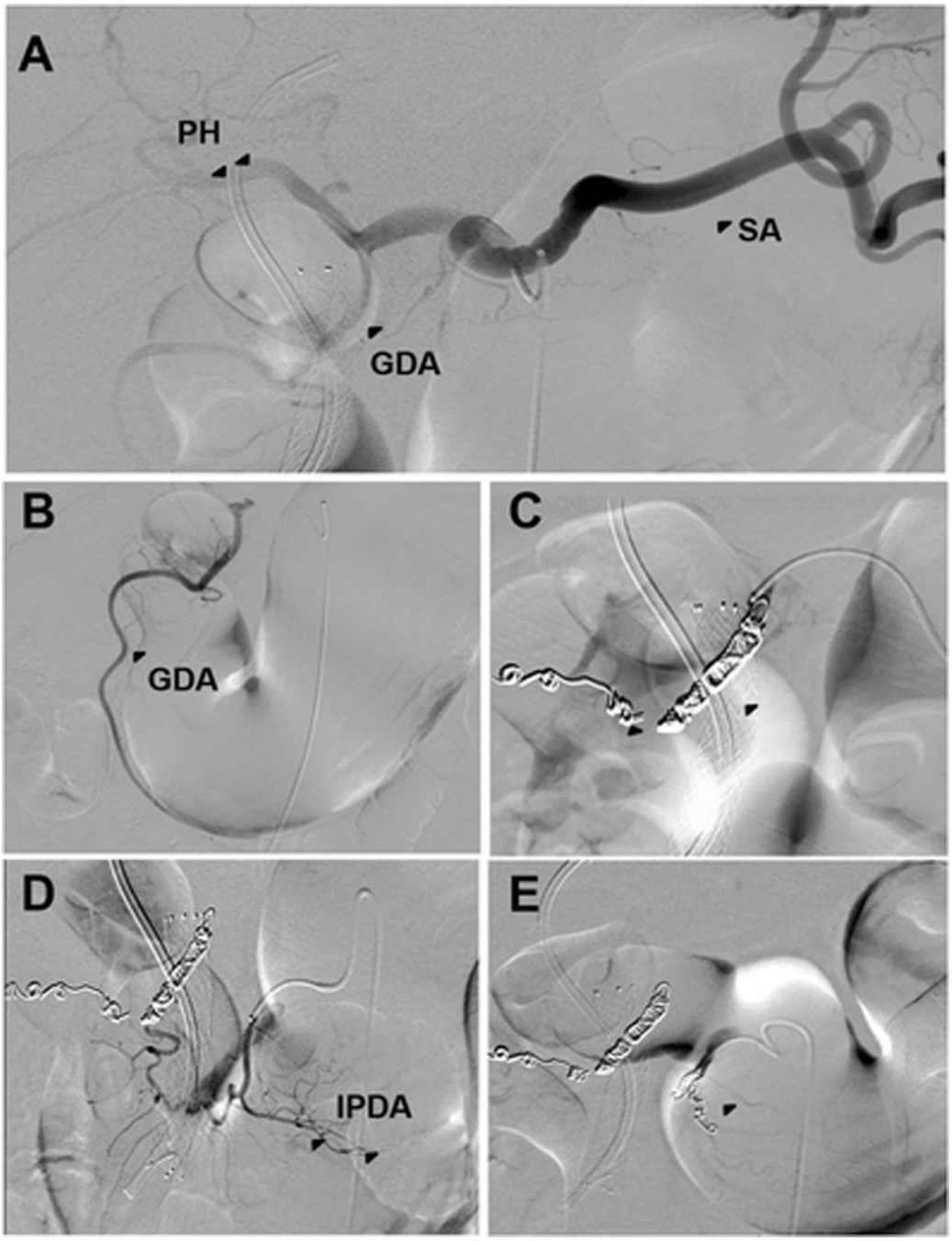

Figure 1.

Re-vascularization protocol of the head of the pancreas of patients enrolled onto the RECLAP trial: hemodynamic changes following peri-pancreatic arterial collateral embolization and catheter placement prior to selective regional chemotherapy administration. A) Celiac arteriogram showing gastroduodenal artery (GDA), proper hepatic artery (PH), and splenic artery (SA) prior to vascular redistribution. B–C) Arteriogram of gastroduodenal artery (arrows) prior to embolization (B) and following coil embolization (C,

arrows). D–E) Arteriogram of inferior pancreatoduodenal artery (arrows) prior to embolization and following coil embolization.

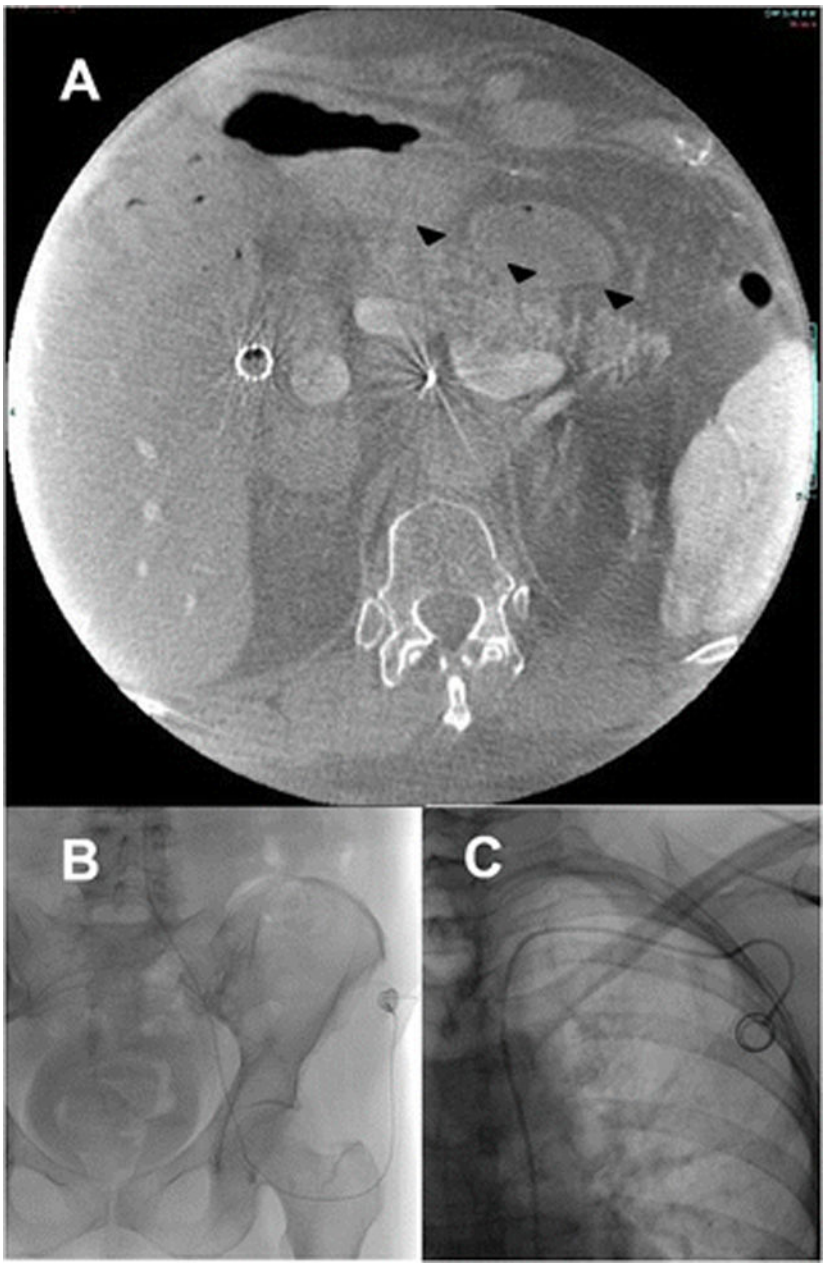

Figure 2.

Post-embolization arterial phase cone beam CT images of the pancreas and port placement. A) Arterial phase cone beam CT images following injection of the splenic artery catheter with contrast. Pancreatic glandular enhancement (arrows) and splenic enhancement. B/C) Femoral and subclavian arterial port and infusion catheter placement. In cases where celiac encasement or tortuosity precluded advancement of the catheter into the splenic artery, splenic artery access for the perfusion catheter was achieved via left subclavian artery catheterization. A left infraclavicular subcutaneous pocket was created for the Celsite port (C).

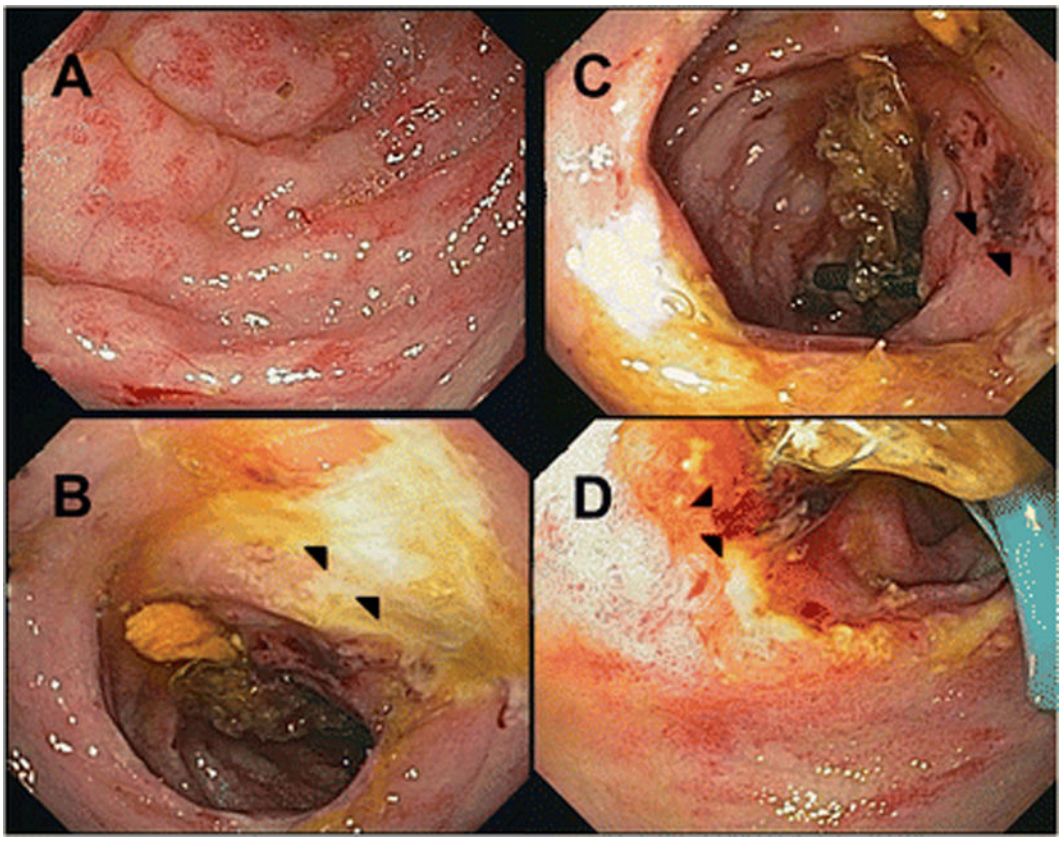

Figure 3.

Upper gastrointestinal bleeding related to duodenal ischemia was observed in two patients resulting in dose limiting grade 3 toxicities. A) Upper endoscopy of patient 4 shows duodenal enteritis in D1 36 hours following continuous infusion of super-selective gemcitabine at 115mg/m2. B) Several ulcerative lesions were covered with bile-tinged fibrin (arrows). C) Areas of ischemia in the duodenal mucosae (arrows) D) Active bleeding in the periampullary region (arrows).

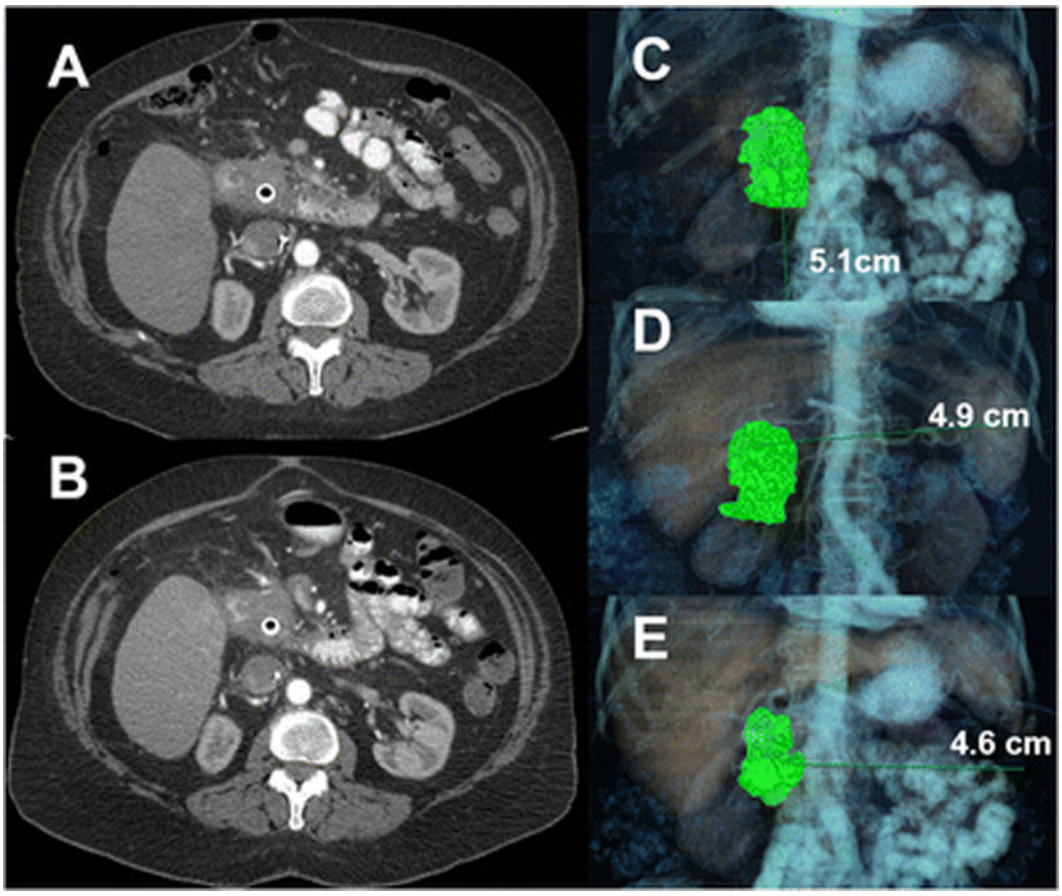

Figure 4.

Two patients with PDAC had stable disease. A/B) Representative computed topography images of patient 2 prior to regional infusion of gemcitabine (A) and following eight cycles of intra-arterial pancreatic gemcitabine infusion. C–E) 3D reconstructed tumor measurement images of patient 2 at the beginning of treatment (C), two months (D), and four months (E) after starting treatment after having received eight cycles of increasing intra-arterial gemcitabine infusions. The patient had an 8% reduction in tumor volume during treatment and was taken to the operating room where a pancreaticoduodenectomy with R0 resection was performed.

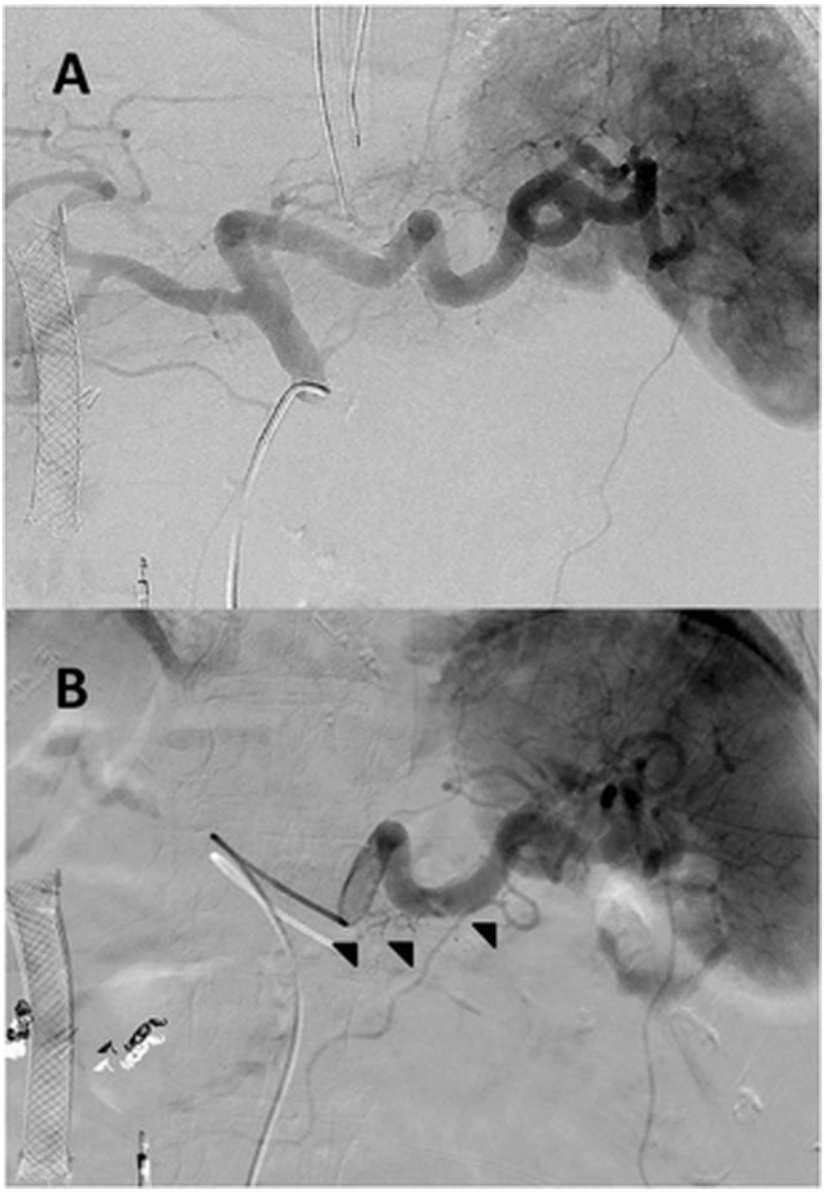

Figure 5.

Neovessel formation four months after vascular redistribution following embolization of peripancreatic arterial collaterals to the pancreatic head and start of gemcitabine perfusions. A) Celiac angiogram demonstrating splenic artery and pancreatic branches prior to hemodynamic change B) Celiac angiogram with neovessel formation (black arrows) four months after hemodynamic change and eight cycles of gemcitabine.

Table 1

Patient demographics prior to enrollment in the RECLAP study.

Patient N°	Age at diagnosis	Gender	Race	ECOG Status	Pancreatic Tumor Location	Initial CA19-9 (units/ml)	Time since diagnosis (m)	No. of prior chemotherapy regimens	Prior RT	Prior Surgical exploration
1	65	Male	Caucasian	0	head	257.0	6	2	Yes	No
2	63	Female	Caucasian	0	head	<1.0	16	1	Yes	Yes
3	68	Female	Caucasian	0	head	106.0	11	1	Yes	No
4	76	Male	Caucasian	0	head	160.0	6	1	No	No
5	56	Female	Caucasian	0	head	7.3	5	1	Yes	Yes
6	71	Female	Caucasian	1	head	521.1	13	1	No	Yes

Table 2

Number of gemcitabine cycles administered and grade three or higher adverse events (ALT, alanine aminotransferase; Alk phos, alkaline phosphatase).

Patient N°	No. of Cycles Completed					Toxicity	
	18mg/m2	36mg/m2	72mg/m2	96mg/m2	115mg/m2	Type	Grade
1	2	2	0	0	0	Anemia	4
2	2	2	2	2	0	none†	–
3	2	2	0	0	0	ALT/Alk phos	3
4	2	2	2	2	1	Anemia, Duodenal Ulcer, Gastro-paresis	3
5	0	2	2	0	0	None	–
6	0	2	2	0	0	Nausea, Fatigue	3

†Grade 3 anemia following pancreaticoduodenectomy

Table 3

Efficacy of regional chemotherapy and survival of patients following treatment.

Patient N°	Best Response	Surgical Resection	Time to Progression (months)	Site of Recurrence	Survival (months)	Cause of Death
1	SD	No	2	Systemic	3	DOD
2	SD	Yes	15	–	15.6	Pulmonary Embolism
3	PD	No	1	Systemic	15	DOD
4	SD	Yes*	22+	–	11+	–
5	PD	No	2	Systemic	16.8	DOD
6	PD	No	2	Systemic	3.8	DOD