Prolonged Infusion of Low Dose Gemcitabine in Advanced Pancreatic Carcinoma

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Abstract

Background: Gemcitabine was established as a monotherapy or in combination for locally advanced or metastatic pancreatic carcinoma. **Aim:** This study aimed to evaluate the efficacy of the low-dose gemcitabine over 6-hour infusion in patients with advanced pancreatic adenocarcinoma. **Methods:** 26 patients with locally advanced or metastatic pancreatic carcinoma were recruited into the study from December 2013 to October 2014. Patients received the treatment in Clinical Oncology Department, Sohag University, and Medical Oncology Department, Assiut University. Patients received low-dose gemcitabine (250 mg/m^2) over 6-hour infusion, weekly for seven weeks and then on days 1 and 8 every 3 weeks till unacceptable toxicity or progression of the disease. **Results:** Twenty-six patients were enrolled in this study. After starting 7 weeks of treatment, the disease control rate was 38.5% in the form of complete response in 3.8% of patients, partial response in 26.9%, and stationary response in 7.7%. However, disease progression occurred in 61.5%. Progression-free survivals were 65.38%, 23.07%, 7.69% and 3.84% after 3, 6, 9 and 12 months, respectively. Also, overall survivals at 3-month, 6-month, 9-month, and 12-month were 61.53%, 42.30%, 23.07%, and 7.69%, respectively. **Conclusion:** Prolonged infusion of low dose gemcitabine is a tolerable and a good option in locally advanced or metastatic pancreatic carcinoma. There may be a benefit of that protocol in patients with bad performance status. More clinical trials with a combination of other cytotoxic agents or target therapy are needed to get better survival and lesser toxicity.

Keywords

Gemcitabine, Pancreatic Cancer, Intravenous Infusion, Low-Dose

1. Introduction

Incidence of pancreatic carcinoma increased in USA, possibly because of in-

creasing obesity, aging, and other causes [1]. Pancreatic cancer is the fourth most common mortality cancer related death among cancer patients [2]. Most patients who develop pancreatic adenocarcinoma, live less than 12 months with the length of patient survival greatly affected by disease stage at presentation, although few other markers of survival have been well characterized [3] [4]. Gemcitabine is an important treatment with 5-FU in locally advanced or metastatic pancreatic carcinoma; NCCN 2018 panel recommends gemcitabine as one option for 1st line therapy [5] [6]. Continuous infusion of gemcitabine provided longer median survival compared with standard 30 minutes infusion, but with increased the risk of hematological toxicities [7]. In phase II study performed by Khaled *et al.*; 2008 in Egypt, 6 hours infusion of gemcitabine and cisplatin was an effective therapy for advanced cancer bladder; myelosuppression was mild. They concluded that the prolonged infusion of gemcitabine deserves to be tested in other malignancies [8]. There is no difference in survival between combination of gemcitabine with other cytotoxic agents and gemcitabine alone [9]. FOLFIRINOX regimen showed a survival benefit, but with increasing in toxicity, this option should be used for the treatment of patients with good performance status [10]. The study was performed to assess the outcome of patients with locally advanced or metastatic pancreatic carcinoma when treated with prolonged infusion of low dose gemcitabine.

2. Methods

During the period from December 2013 to October 2014, twenty-six patients with locally advanced or metastatic pancreatic carcinoma were recruited in this study from Clinical Oncology Department, Sohag University and Medical Oncology Department, Assiut University. Eligibility criteria included patients with 18 years or more, both sexes, performance status ECOG (0-2), with good organs functions. No Pregnancy or lactation was allowed during period of chemotherapy and fertile patients had to use effective contraception. We did pretreatment evaluation included history, clinical examination, laboratory tests (complete blood counts, kidney function, liver function, tumor marker CA19-9), and radiological studies (abdominal ultrasonography, chest x-ray and multi-slice computed tomography (CT) of the abdomen and pelvis). After complete work up, patients were clinically staged before treatment according to TNM clinical staging system.

Treatment plan consisted of continuous infusion of gemcitabine at a dose of 250 mg/m^2 over 6 hours infusion given in weekly for seven weeks and then on day 1 and day 8 every 3 weeks until there is disease progression or unacceptable toxicity. Doses were adjusted according to blood counts, withheld if: Absolute neutrophilic count is <1500/ul or platelets count < 75,000/ul on day 1 or if creatinine level > 1 time (×) upper normal limit (UNL) or aspartate aminotransferase > 5 × UNL or bilirubin level > 1.5 × UNL. In this case, laboratory investigations were repeated weakly and chemotherapy was restarted again as soon as counts allowed, with at least 50% of the dose to be administered. The patients were

followed up by history, physical examination, CBC, chemistry, liver function test every cycle. After 7 weeks of continuous infusion of gemcitabine, patients were followed by multi-slice CT of chest & pelvi-abdominal and tumor marker CA 19-9. If there was radiological or biochemical response (partially or stationary), treatment was continued as day 1 and day 8 every 3 weeks then assessment by CT of chest & pelvi-abdominal and tumor marker CA 19-9 every three cycles. If there was radiological or biochemical progression during treatment, we shifted to second line of chemotherapy (combination chemotherapy). We classified our patients according their demographics (age, gender, body mass index and performance status) and tumor characteristics (tumor site, tumor size, tumor grade, metastatic status, and CA 19-9 level).

Statistical methods of analysis:

Data collected and analyzed by computer program SPSS "ver. 21". The primary end-points were progression-free survival (PFS), which was defined as the time from the start of treatment to disease progression or death from any cause, whichever came first. Secondary end-points were overall survival (OS) and disease control rate (DCR). OS was defined as the time from the start of treatment to date of death from any cause, or date of last follow up, whichever came first. Disease control rate (DCR) was defined as sum of rates of stable disease (SD), complete response (CR), and partial response (PR). Univariate analysis was used through the presentation of continuous variables as median and range. Categorical variables are presented as frequency and percentage. Bivariate analysis was done to compare categorical variables using Chi-Square test or Fisher Exact test when appropriate. Kaplan-Meier method was used to estimate the survival time distribution and the median survival. The treatment difference between two groups was assessed by a log-rank test. A P-value less than 0.05 is considered as a cut-off.

3. Results

From December 2013, to October 2014, we enrolled 26 patients treated in Clinical Oncology Department, Sohag University and Medical Oncology Department, South Egypt Cancer Institute, Assiut University. Overall, 19 patients were male (73.1%), and 7 patients were female (26.9%) with a median age of 57.6 years (range 19 - 81). Forty-two percent (42.3%) of patients were nonsmokers. Their main complains were abdominal pain (100%) then jaundice (80.76%) (Table 1).

As regard disease characteristics, pathological diagnosis of T3 and T4 were 57.6% and 15.4%; respectively. Twenty-one of patients (80.76%) had tumor at the head of pancreas, three patients (11.5%) at the tail, two patients (7.7%) at the body of pancreas. Eleven patients (42.3%) were stented to relieve the obstructive jaundice. Sixty-five percent of patients had a solitary site of metastasis, which was the liver. While there were only five percent of patients had multiple sites of metastases, which included liver, lung, and bone (Table 1).

After treatment of 26 patients with continuous infusion of gemcitabine over 6-hour infusion weekly for seven weeks and then for day 1andday 8 every 3 weeks, there was disease control rate of 38.5% in the form of complete response

in one patient (3.8%), partial response in 7 patients (26.9%) and stationary response in 2 patients (7.7%), while there was a disease progression in 16 patients (61.5%) (Figure 1).

Table 1. Demographics and baseline characteristics of enrolled patients (n = 29) receiving gemcitabine of low dose over 6-hour infusion.

Characteristic	No	%
Age, Years		
Mean (Range)	57.69 (19 - 81)	
Sex		
Male	19	73.1%
Female	7	26.9%
Diabetes Mellitus		
Type I	2	7.7%
Type II	12	46.2%
Non	12	46.2%
BMI		
Obese	1	3.8%
Average	7	26.9%
Under built	13	50.0%
Cachectic	5	19.2%
ECOG PS		
Grade 0	1	3.8%
Grade I	14	53.8%
Grade II	11	42.3%
Clinical Manifestation		
Abdominal pain	26	100%
Jaundice	21	80.8%
Pruritis	3	11.5.7%
Nausea & vomiting	2	7.7%
Pancreatic Tumor Site		
Head	21	80.76%
Body	2	7.7%
Tail	3	11.5%
Multicentric	0	0.0%
Tumor Size		
T2	7	26.9%
T3	15	57.6%
T4	4	15.4%
Tumor Grade		
Grade I/II	17	65.4%
Grade III	6	23.1%
Unknown	3	11.5 %
Presence of Metastasis		
Solitary	17	65.4%
Multiple	5	19.2%
Non	4	15.4%
CA19-9 level		
Normal	9	34.6%
High	17	65.4%

Abbreviations: BMI, Body Mass Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
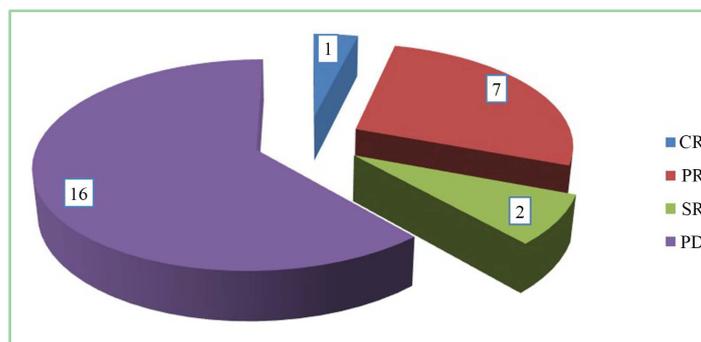
Figure 1. Pia chart of response rates in study group. CR, complete remission; PD, progressive disease; PR, partial remission; SR, stationary response.

Hematological toxicity was the most significant adverse effect. Grade 3 and 4 neutropenia were observed in 8 (36.7%) and 4 (15.4%) patients, respectively. Grade 2, 3, and 4 anemia occurred in 9 (34.6%), 13 (50%), and 2 (7.7%) patients, respectively. Grade 2 thrombocytopenia occurred only in 2 (7.7%) patients. Also, non-hematological toxicity was observed such as increased creatinine level in 6 (23.0%) patients, nausea occurred in all patients (100%), vomiting grade 1, 2, and 3 experienced in 4 (15.3%), 12 (46.1%), 5(19.2%) patients; respectively. Diarrhea grade 1 and 2 are observed in 12 (46.1%), 4 (15.3%) patients; respectively. Six (23%) patients experienced alopecia (Table 2).

Mean progression-free survival (PFS) was 3.65 months, 95% CI 2.34 - 4.95 months (Figure 2). Progression-free survival at 3-month, 6-month, 9-month, and 12-month were 65.38%, 23.07%, 7.69%, and 3.84%, respectively (Table 3). The mean overall survival (OS) was 5.69 months, 95% CI 4.34 - 7.52 months (Figure 3). Overall survival at 3-month, 6-month, 9-month, and 12-month were 61.53%, 42.30%, 23.07%, and 7.69%, respectively (Table 3). Performance status was significantly correlated with PFS (P-value < 0.01). While other factors which were theage, the tumor size, the tumor grade, the tumor marker CA19-9, body mass index, and smoking were not significant either for PFS or OS.

4. Discussion

In the present study, the median of age was 59 years (range 19 - 81) with peak incidence in 5th decade and 6th decade; 7 cases (26.9%) per each, and that was comparable with series of Tempro *et al.*, 2003 in which the median of age was 62 years and the peak of incidence was in 6th decade [11]. Poplin *et al.* observed that peak incidence was in the fifth and sixth decades of life [12]. Regarding disease control rate, it was 38.5%, which is comparable with study conducted by Poplin *et al.*, in which response rate was 36%.

The overall survival in this study was 5.69 months, 95% CI 4.34 - 7.52 months and 12-month survival was 7.69% and that was less than reported by Poplin *et al.* [12], in which single-agent gemcitabine (GEM) 1000 mg/m^2 over 30-minute infusion compared with fixed-dose rate (FDR) GEM 1500 mg/m^2 over 150-minutes and GEM 1000 mg/m^2 over 100-minutes infusion/day 1 plus oxaliplatin 100 mg/m^2/day

2 every 14 days (GEMOX) . The median survival and 1-year survival were 4.9 months and 16% for GEM, 6.2 months, and 21% for GEM FDR (P = 0.04), and 5.7 months and 21% for GEMOX (P = 0.22). This contrast may be due to different biological capacity of the patients or different treatment schedule and dosage. As patients with good performance status (PS 0, 1) were higher than those in our study (more than 80% of the patients in the three groups of Poplin's study versus 57.6% in our study.

Table 2. Toxicities according to CTCAE (version 4.03) in 26 patients.

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Neutropenia	-	-	8 (30.7%)	4 (15.3%)
Anemia	-	9 (34.6%)	13 (50%)	2 (7.7%)
Thrombocytopenia	5 (19.2%)	2 (7.7%)	-	-
Non-Hematological				
Creatinine	2 (7.7%)	4 (15.3%)	-	-
Nausea	6 (23.0%)	14 (53.8%)	6 (6.6%)	-
Vomiting	4 (15.3%)	12 (46.1%)	5 (19.2%)	-
Diarrhea	12 (46.1%)	4 (15.3%)	-	-
Alopecia	6 (23.0%)	-	-	-

Abbreviation: CTCAE, the Common Terminology Criteria for Adverse Events.

Table 3. Distribution of Progression-Free Survival (DFS) and Overall Survival (OS) of all patients in the follow up period (12 months), presented as number of patients and their percent.

Survival category	3 months	6 months	9 months	12 months
PFS	17 (65.38%)	6 (23.07%)	2 (7.69%)	1 (3.84%)
OS	16 (61.53%)	11 (42.3%)	6 (23.07%)	2 (7.69%)

Abbreviations: OS, Overall Survival; Progression-Free Survival (PFS).
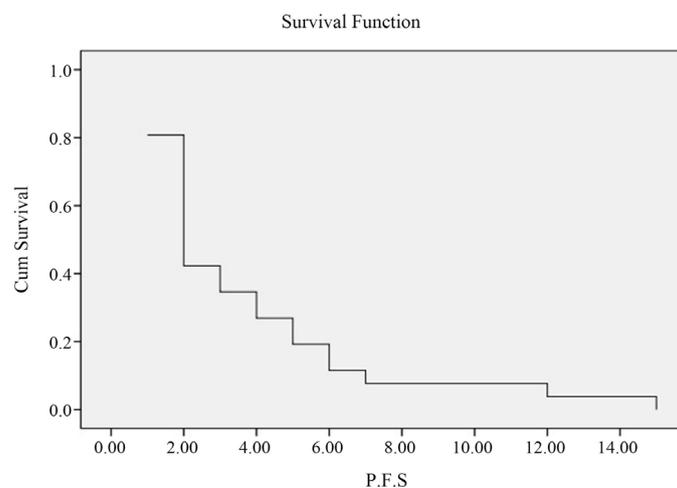
Figure 2. Kaplan-Meier plot of progression-free survival.
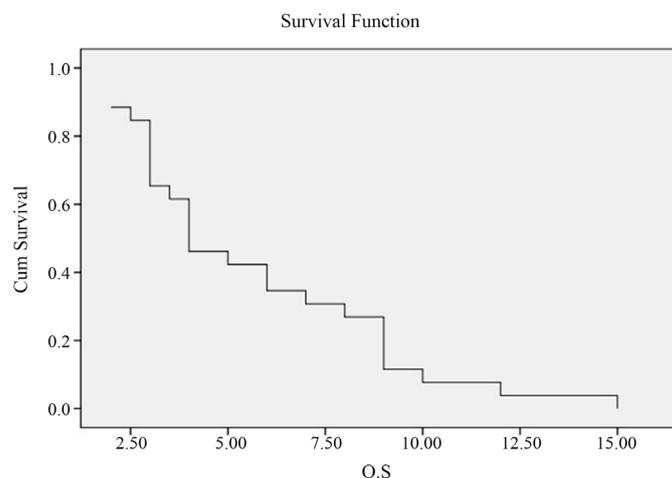
Figure 3. Kaplan-Meier plot of overall survival.

The treatment was subjectively well tolerated in the present study, although hematological toxicity was the most significant adverse effect. Grade 3, 4 neutropenia observed in 8 (36.7%), 4 (15.4%) patients respectively. Grade 3 and 4 anemia occurred in 13 (50%) and 2 (7.7%) patients; respectively, while grade 1 and 2 thrombocytopenia occurred in 5 (19.2%) and 2 (7.7%) patients; respectively. These incidence rates were less than that of Tempro *et al.* [11] in which grade 3/4 thrombocytopenia, grade 3/4neutropenia, and grade 4 anemia were observed in FDR arm as follows: 37%, 48.8%, 9.3%; respectively.

Also, our incidence rates of toxicities were less than that reported by Poplin *et al.* [12] in which the most significant toxicity was myelosuppression, which was worse in GEM FDRarm. As they stated that grade 3/4 thrombocytopenia was 33%, neutropenia 3/4 was 59% and anemia 3/4 was 19%. This emphasizes that the low-dose gemcitabine protocol has a lower incidence of toxicity than that caused by standard dose protocol of gemcitabine.

The main limitation of our study is the small sample size, but we did larger randomized phase II study based on the result of this trial [13].

This study was presented as an abstract [14]—not a full paper—on the 2016 ESMO World Congress on Gastrointestinal Cancer was held in Barcelona, Spain; 29 June-2 July 2016. We want to share our practice in this study by publishing it as a full text to be more useful.

5. Conclusion

Prolonged infusion of low dose gemcitabine is a tolerable and a good option in locally advanced or metastatic pancreatic carcinoma. There may be a benefit of that protocol, especially patients with bad performance status. More clinical trials with a combination of other cytotoxic agents or target therapy are needed to get better survival and lesser toxicity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

5-FU: 5-Fluorouracil

BMI: Body Mass Index

CR: Complete Response

CT: Computed Tomography

CTCAE: Common Terminology Criteria for Adverse Events

DCR: Disease Control Rate

ECOG PS: Eastern Cooperative Oncology Group Performance Status

FDR: Fixed-Dose Rate

GEMOX: Gemcitabine plus Oxaliplatin

NCCN: National Comprehensive Cancer Network

OS: Overall Survival

PFS: Progression-Free Survival

PR: Partial Remission

PR: Partial Response

SD: Stable Disease = SR: Stationary Response

TNM: Tumor (T), Nodes (N), and Metastases (M)

UNL: Upper Normal Limit