Platinum based combination versus single agent gemcitabine in Metastatic Pancreatic Cancer

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Abstract: Background and aim: Majority of pancreatic cancer patients was diagnosed with metastatic disease with a very poor prognosis, our study aimed to assess treatment toxicity and compare response rate (RR), overall survival (OS) and Progression free survival (PFS) in platinum based combination versus single agent gemcitabine. **Patient and method:** Thirty five patients pathologically confirmed to have metastatic pancreatic adenocarcinoma during period (2012-2014). Patients were randomly assigned into three groups: platinum based regimens **group A**: Gemcitabine and Oxaliplatin (Gem Ox), **group B**: Gemcitabine and cisplatin and **Group C**: single agent Gemcitabine. **Results:** mean age was 52.5 years ,with nearly equal sex affection the main presenting symptoms was epigastric pain in 77% of patients and the main presenting sign was jaundice in 66% of patients. CA19-9 was elevated in 74% of patients and cancer head of pancreas was the most common site in 77% of patients. The most common pathology was moderately differentiated adenocarcinoma 51.4% of patients. The median OS was prolonged, with an increase of 4 months in the group of (Gemzar and Cisplatin) when compared with the gemcitabine group (8 vs.4 months) or an increase of 2 months in comparison with Gem Ox (8 vs. 6 months), also median PFS was significantly prolonged compared with the gemcitabine group (6 vs.3 months) or in comparison with Gem Ox (6 vs. 5 months) (***P*-value** 0.017)**.** RR in (Gemzar and Cisplatin) was higher in comparison with Gem Ox (40% vs. 30%) and with the single agent gemcitabine group (40% vs.8%) with a statistically significant difference. **Conclusion**: (Gemzar and Cisplatin) was an effective first line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status ,with improved OS and PFS. Patient age alone should not be a factor in treatment decision making.

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1. Introduction:

Worldwide, pancreatic cancer is the eighth leading cause of cancer deaths in men (138,100 deaths annually) and the ninth in women (127,900 deaths annually) [(1)].

Risk factors for cancer of the pancreas include age (a 50 years and older), male sex, race (black), smoking, diet high in meats and fat, presence of diabetes or chronic pancreatitis, exposure to chemicals in the work-place, and a family history.

Only about 10% to15% of patients who present with pancreatic cancer are considered eligible for resection and most cases of pancreatic cancer are advanced at the time of diagnosis Stage IV [(2, 3)].

Patients diagnosed with Stage IV pancreatic cancer can be broadly divided into two groups: ***Stage IVA pancreatic cancer*** (localized or locally advanced) is locally confined, but involves adjacent organs or blood vessels, thereby hindering surgical removal. ***Stage IVB pancreatic cancer*** (metastatic) has spread to distant organs, most commonly the liver.

Historically, patients with metastatic pancreatic cancer have been considered incurable and rarely survived more than one year. With newer treatments, some patients are surviving 1-2 years and can experience improved quality of life. Treatment options for stage IV pancreatic cancer include the following either:

Palliative therapy (Pain- reliever, supportive care and Palliative surgical biliary bypass, percutaneous biliary stent placement, or endoscopically placed biliary stents) or chemotherapy [(4-6)].

Currently, the standard chemotherapy drug for the treatment of advanced pancreatic cancer is Gemzar, which has been shown to improve response to treatment, time to cancer progression, and survival duration when compared with the older chemotherapy drug 5-fluorouracil.1 In a clinical trial comparing Gemzar to 5-FU, Gemzar produced significant improvement in disease-related symptoms, as well as prolonging survival. The number of patients surviving one year after treatment with Gemzar was 18%, compared with only 2% with 5-FU [(7)].

Associations of gemcitabine with fluoropyrimidines (i. v. or oral) or platinum derivatives (cisplatin or oxaliplatin) obtained a significant improvement in overall survival only in meta-analyses [(8)].

among the several evaluated targeted drugs, only erlotinib was able to obtain, when combined

with gemcitabine, an increase in overall survival, but this advantage is very modest (2 weeks only) [9].

On the basis of international phase III trial (NCT00844649l), nab-paclitaxel plus gemcitabine is a standard treatment option for patients with advanced pancreatic cancer [10], but this study does not address the efficacy of nab-paclitaxel-gemcitabine versus FOLFIRINOX.

FOLFIRINOX versus gemcitabine: A multicenter phase II/III trial. The median overall survival (OS) was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group and Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group but FOLFIRINOX was more toxic than gemcitabine [11].

Based on currently available data no standard second line treatment exist, however in the CONKO-003 trial, patients who failed gemcitabine first line were shown to have better OS if they received OFF regimen, other option include XELOX which is likely to produce outcome similar to OFF regimen [12-16].

A targeted therapy is one that is designed to treat only the cancer cells and minimize damage to normal, healthy cells. Cancer treatments that "target" cancer cells may offer the advantage of reduced treatment-related side effects and improved outcomes.

Researchers from Brown University have found that treatment of patients with advanced pancreatic cancers that over express HER2 with Gemzar plus Herceptin appears to produce longer survival than treatment with Gemzar alone. Approximately 72% of patients treated with the combination demonstrated an anticancer response. Approximately 24% of patients lived one year or more following treatment [17].

Researchers from the M.D. Anderson Cancer Center have reported that the addition of Erbitux to Gemzar may improve survival for patients with advanced pancreatic cancer. This trial involved 40 patients with advanced pancreatic cancer who had tested positive for over expression of EGFR. Results indicate that more of the patients who received Gemzar plus Erbitux lived one year or more and were cancer-free for longer than patients who were treated with Gemzar alone .(Table 2). [18]

2. Patients and method:

Patient Characteristics, Thirty five patients pathologically confirmed to have metastatic pancreatic adenocarcinoma during period (2012-2014) in Assuit University Hospital with the following eligibility Criteria: ECOG performance status of 0 to 2 was required. Patients had to have adequate baseline organ function including WBC ≥ 3,500/mm3, absolute neutrophil count ≥ 1,500/mm3, platelets ≥ 125,000/mm3, bilirubin lower than 2.0 mg/d L, AST lower than 3.0× upper limit of normal, creatinine ≤ 1.5× upper limit of normal. Women could be neither pregnant nor breast feeding.. Patients with other active illnesses were excluded as well as those with symptomatic peripheral neuropathy ≥ grade 2 and all patients signed informed consent .

Treatment: Patients were randomly assigned into three groups:

Platinum based regimens (**Group A**: GEMOX (GEM 1,000 mg/m^2 over 100 minutes 10 mg/m^2/min] day 1 and oxaliplatin 100 mg/m^2 day 2 over 120 minutes every 14 days cycle**. Group B:** GEM 1,000 mg/m^2 over 30 minutes day 1,and cisplatin 50 mg/m^2 over 60 minutes day 1 every two weeks.). **Group** C: GEM (the first cycle of GEM at 1,000 mg/m^2 as a 30-minute infusion weekly for 7 weeks followed by 1 week of rest; for the subsequent cycles received cycles of single agent GEM 1,000 mg/m^2/30 minutes weekly for 3 weeks followed by 1 week rest). All patients completed a symptom assessment before therapy, and after 8 and 16 weeks. Treatment modifications were mandated for myelosuppression or grade 3/4 toxicity. Patients requiring doses to be withheld on two or more consecutive occasions were removed from study. Patients requiring a decrease in GEM dose to lower than 500 mg/m^2 were removed from study.

Oxaliplatin was held for patients with persistent grade 3 or 4 neuropathy or other oxaliplatin-related symptoms, and such patients then could continue to receive 30-minute infusion GEM alone weekly for 3 weeks followed by 1 rest week. All patients who received a single dose of assigned chemotherapy were assessable for efficacy and toxicity. Patients who progressed during the first 8 weeks of study were considered non responders. Patients were removed from study at the time of progressive disease. Patients removed from study for any reason were observed for 4 weeks after the last dose of chemotherapy for toxicity assessment and until death for survival duration. Patients with stable disease, or partial or complete remission were eligible to continue therapy on study until disease progression or intolerable toxicity occurred.

Response Evaluation Criteria in Solid Tumors were utilized for response assessment at 8-week intervals. All responses had to be confirmed by repeat assessment at ≥ 4 weeks. The aim of this study was to the assess treatment toxicity, comparison of response rate, overall survival and disease free survival in the three arms.

Statistical considerations:

OS and PFS curves were obtained using the Kaplan-Meier method. OS was defined as the time from random assignment to death, or censored at last known date of survival. PFS was defined as the time from random assignment to progression, or death without evidence of progression.

3. Results:

Thirty five patients were included in this study their age range (24-75) and the mean age was 52.5 years, with nearly equal sex affection. The main presenting symptom was epigastric pain 77% and the main presenting sign was jaundice in 66%. ERCP with stent replacement was done in 43% to relief jaundice. CA19-9 was elevated in 74% of patients and cancer head of pancreas was the most common site 77%, followed by 14% body and tail of pancreas and 8% tail of pancreas. The most common pathology was moderately differentiated adenocarcinoma 51.4% followed by poorly differentiated adenocarcinoma in 31.4% and well differentiated adenocarcinoma in 17.1% **(Table 1)**.

Patients were randomized into three groups group A&B received platinum based combination with gemcitabine and group C received single agent gemcitabine **(Table 2).**

Response rate was 30%, 40%, 8% in group A, B, C respectively **(Table 3)**. One year survival rate was 40%, 30%, 20% in group A,B, C respectively ,median overall survival was 6,8, 4 months in group A,B,C respectively with a statistically non-significant difference ***(***P-value 0.287). **(Table 4)**. PFP 5, 6, 3 months in group A, B, C respectively with a statistically significant difference ***(***P-value 0.017). **(Table 5)**

As regard treatment toxicity, overall, 32 patients (100%) experienced at least one adverse event AE during this study. The most commonly reported AEs during this study were abdominal pain (78%) which is more in group A, anorexia & weight decrease in (62%), vomiting (53%), nausea (75%) and diarrhea (47%).nausea &vomiting more in group B 28%,25% of patients respectively,

Neutropenia was observed in 65.6% of patients, neutropenia was observed more in group B 28% of patients, anemia was observed in 28% of patients, thrombocytopenia was observed in 25% of patients. Peripheral neuropathy was observed in 15.6% of group A **(Table 6).**

Table (1): Patients characteristic

	No. (n= 35)	%
Age: Mean ± SD (Range)	52.51 ± 11.17 (24.0 – 75.0)	
< 60 years	26	74.3
≥ 60 years	9	25.7
Sex:		
Male	18	51.4
Female	17	48.6
Main symptoms:		
Epigastric pain	27	77.1
Main sign:		
Jaundice	23	65.7
CA 19.9:		
Low	9	25.7
High	26	74.3
Site of malignancy:		
Head of pancreas	27	77.1
Body and tail of pancreas	5	14.3
Tail of pancreas	3	8.6
Histopathology:		
Moderately differentiated adenocarcinoma	18	51.4
Poorly differentiated adenocarcinoma	11	31.4
Well differentiated adenocarcinoma	6	17.1

Table (2): First line of treatment

First line of treatment	No. (n= 35)	%
Gem ox	10	28.6
Gemzar, cisplatin	10	28.6
Weekly gemzar	12	34.3
Missed	3	8.6

Table (3): Response rate to treatment

Treatment	No.	Response rate %
Gem ox	3/10	30
Gemzar, cisplatin	4/10	40
Weekly gemzar	1/12	8

Table (4): Means and Medians overall Survival Time in the three groups

First line of treatment	Mean ± SE	Median	*P*-value
Gem ox	7.90 ± 1.20	6.0	0.287 ns
Gemzar, cisplatin	8.10 ± 1.12	8.0	
Weekly gemzar	5.67 ± 1.04	4.0	

Table (5): Means and Medians progression free Survival Time in the three groups

First line of treatment	Mean ± SE	Median	*P*-value
Gem ox	6.00 ± 0.89	5.0	0.017*
Gemzar, cisplatin	6.10 ± 0.81	6.0	
Weekly gemzar	3.67 ± 0.61	3.0	

Table (6): Treatment toxicity

Treatment toxicity	No. (n= 32)	%
Abdominal pain	25	78.1
Nausea	24	75.0
Anorexia	20	62.5
Vomiting	17	53.1
Diarrhea	15	46.9
Weight loss	20	62.5
Neutropenia	21	65.6
Anemia	9	28.1
Thrombocytopenia	8	25.0
Peripheral neuropathy	5	15.6

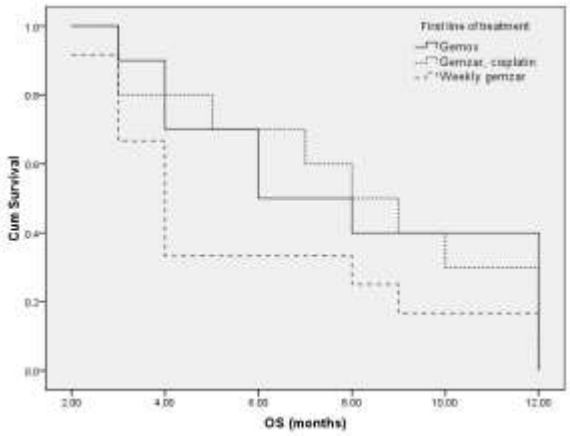

Figure (1): overall Survival Time in the three groups

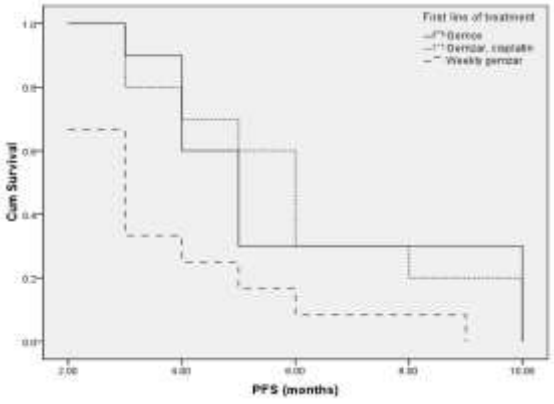

Figure (2): progression free Survival Time in the three groups

4. Discussion:

In our study, (Gemzar & Cisplatin) was an effective first line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status. The median overall survival was prolonged, in the group of (Gemzar & Cisplatin) when compared with the gemcitabine group (8 vs. 4 months) or in comparison with Gem Ox (8 vs. 6 months), also median PFS was significantly prolonged compared with the gemcitabine group (6 vs. 3 months) or in comparison with Gem Ox (6 vs. 5 months) *P*-value (0.017*).

As regard response rate: Gemzar and Cisplatin had a higher response rate in comparison with Gem Ox (40% vs. 30%) and statistically significant difference with the gemcitabine group (40% vs. 8%). Comparison of the results of (Gemzar and Cisplatin) in our study with the results in other trials with similar agents or different agents like Gemzar/ Alimta, showed a higher Response Rate, 1-year survival rate and overall survival [19, 20], while in comparison with FOLFIRINOX and nab-paclitaxel plus gemcitabine both had a longer overall survival (11.1 and 8.5 months) than with (Gemzar and Cisplatin)in our study [23, 24].

Table (7): results of different trails in treatment of metastatic pancreatic cancer

	Response rate	1-year survival	Overall survival
Gemzar/ Platinol [19]	26%	NA***	7.5 months
Gemzar/ Alimta [20]	15%	30%	6.5 months
Gemzar/ Eloxatin [21]	31%	47%	NA
FOLFIRINOX [23]	31.6%	48.4%	11.1 months
Nab-paclitaxel plus gemcitabine [24]	23%	35%	8.5 months
In our study:			
Gem ox	30%	40%	6 months
Gemzar, cisplatin	40%	30%	8 months
Weekly gemzar	8%	20%	4 months

In recent years more oncologists are using single agent gemcitabine for treating elderly patients with metastatic pancreatic cancer compared to 15 years ago [25]. In order to improve the outcome, many clinical trials have looked into combining gemcitabine with other agents. While overall these combinations have resulted in slight increase in overall survival, but the associated increased toxicity has limited their use in elderly metastatic cancer patients [26].

It is still important to emphasize that patient age alone should not be a factor in treatment decision making. There has been emerging evidence on role of geriatric assessment in predicting chemotherapy toxicity in elderly cancer patients [27].

In our study elderly patients (60-75 years) were included in combined treatment groups (A and B) with a higher response rate and overall survival rate and prolonged PFS in comparison with single agent in group C. Limited increase in treatment toxicity in combined groups (vomiting, and peripheral neuropathy) encourage our recommendation for combined treatment modalities in elderly patients.

Conclusion:

Gemzar & Cisplatin was an effective first line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status with an improved OS & PFS. Patient age alone should not be a factor in treatment decision making.

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