Gemcitabine plus capecitabine versus gemcitabine plus oxaliplatin for patients with advanced pancreatic cancer

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Abstract: Purpose: The purpose of this study was to compare the efficacy and safety of two different chemotherapy regimens in the treatment of advanced pancreatic cancer (PC). **Material and Methods:** Thirty-nine patients with advanced (local advanced and/or metastatic) unresectable pancreatic adenocarcinoma were enrolled in this study and assigned to receive gemcitabine 1000 mg/m^2 intravenous infusion (IVI) on days 1 and 8 plus oral (po) capecitabine 825 mg/m^2 twice daily, days 1–14 followed by a treatment free interval of seven days (Gem-Cap) or gemcitabine 1000 mg/m^2 IVI on days 1 and 8 plus oxaliplatin 130 mg/m^2 IVI on day 8 (Gem-Ox). Treatment cycles were repeated every three weeks. The primary study end point was assessment of the overall survival (OS) rate; secondary end points were, assessment of the progression-free survival (PFS) rate, objective response rate (ORR), and treatment toxicity. **Results:** The median follow up time for all patients was 18 weeks. At the time of final analysis, 35 (89.7%) deaths had occurred. Out of the total 39 patients, there were no complete response (CR), 23.8% in the Gem-Cap arm and 22.2% in the Gem-Ox arm had partial response (PR) while 33.3% and 44.4% had stable disease (SD) respectively. Progressive disease occurred in 42.9% of Gem-Cap arm and in 33.3% of the Gem-Ox arm. Patients assigned to Gem-Ox had apparent but not significant improved overall response rate over Gem-Cap (p=0.759). The 1-year OS rate was 9.52% in the Gem-Cap arm vs. 11.11% in the Gem-Ox arm, (p=0.792). The corresponding median survival time was 18 weeks vs. 17 weeks, respectively (p=0.717). The 1-year PFS rate was 4.76% in the Gem-Cap arm and 8.33% in the Gem-Ox arm, (p=0.715). Median PFS was estimated with 15 weeks and 14 weeks, respectively (p=0.388). Grade 3/4 hematological toxicities were more frequent in the Gem-Cap arm than Gem-Ox arm (28.6% vs. 5.6% respectively, p<0.05). Non-hematological toxicity presented with peripheral neuropathy was more frequent in Gem-Ox arm, p=<0.001, whereas hand-foot syndrome was more in Gem-Cap arm, p=0.001. **Conclusion:** Although our study had the limitation of being a single center study with a small sample of enrolled patients, our results can conclude that, the advanced pancreatic cancer is a fatal disease. The efficacy of the Gem-Ox regimen in the treatment of advanced PC seems to be similar to Gem-Cap regimen. However, the toxicity profile of the Gem-Ox regimen is different with significantly fewer hematological adverse events and the major side-effects were peripheral neuropathy whereas, the hand-foot syndrome being the main non-hematological toxicity in the Gem-Cap arm. Further multi-centers trials with large number of patient comparing different multi-agents' regimens with different dosage schedules for patients with advanced PC are warranted.
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1. Introduction

Advanced pancreatic cancer is a devastating disease. In 2008, there were 213,000 pancreatic cancer patients worldwide and most of these patients died as a result of disease progression.[1] The high mortality rate for this disease reflects typical inoperable states due to early distant metastases and ineffective treatment regimens.

Gemcitabine monotherapy was the standard care for patients with locally advanced and metastatic pancreatic adenocarcinoma.[2] However, patients who receive this therapy have a median overall survival (OS) of only 5.6 months.[3] In an effort to increase the objective response rate (ORR) and the survival rate of locally advanced and metastatic patients, many trials have been carried out to evaluate gemcitabine monotherapy or combination therapy regimens. The National Comprehensive Cancer Network (NCCN) guidelines indicate that gemcitabine combined with one other agent is the optimal treatment for these patients.[4]

Combination regimens based on gemcitabine and capecitabine (oral fluoropyrimidine) have been evaluated in numerous clinical phase I/II trials for advanced pancreatic cancer.[5–8] Promising results were obtained when gemcitabine was combined with capecitabine or with a platinum compound (cisplatin or oxaliplatin) in phase III trials.[9–12]

Also the combination of gemcitabine with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib showed a statistically significant survival benefit for this combination regimen.[13] Thus, the optimal combination chemotherapy regimen for advanced PC still remains to be defined.

2. Patient and Methods

This prospective study was conducted at Clinical Oncology Department, Tanta University Hospital from May 2008 to April 2012, as 39 patients with advanced PC were enrolled in the study**.**

Eligibility Criteria

Patients age >18 years with a histologically, cytologically and radiologically confirmed diagnosis of locally advanced (stage III) or metastatic (stage IV) ductal adenocarcinoma or undifferentiated carcinoma of the pancreas not amenable to treatment with curative intent.

Patients had performance status of 0-2 following the Eastern Cooperative Oncology Group (ECOG) with life expectancy more than 3 months and not received any prior chemotherapy or radiotherapy.

Patients had adequate baseline organ function including total leucocytic count ≥3,500/mm^3, absolute neutrophil count ≥1,500/mm^3, platelets ≥125,000/mm^3, total serum bilirubin <3 mg/dL and serum creatinine ≤1.6 mg/dL and at least one radiographically documented measurable lesion was required.

Exclusion Criteria

Patients with a history of other malignancy, significant cardiac illness, other active illnesses or women that are pregnant or breast feeding were excluded from the study.

Treatment protocol

Patients in the gemcitabine plus capecitabine (Gem-Cap) arm, were treated with gemcitabine 1000 mg/m^2 intravenous infusion (IVI) over 30 min on day 1 and 8 and oral (po) capecitabine 825 mg/m^2 twice daily, days 1–14 followed by a treatment free interval of seven days. Patients in the gemcitabine plus oxaliplatin (Gem-Ox) arm were treated with gemcitabine 1000 mg/m^2 IVI over 30 min on day 1 and 8 and oxaliplatin 130 mg/m^2 IVI over 120 min on day 8. In both treatment arms, courses were repeated every 3 weeks.

According to clinical and laboratory parameters, treatment modifications were mandated for myelosuppression or grade 3/4 non-hematological toxicity. If patients had an absolute neutrophil count <1,000/mm^3, platelet count <70,000/mm^3, or unacceptable non-hematological toxicities (≥grade 3), the start of the next cycle chemotherapy was delayed up to 2 weeks in order to allow for recovery. However, if the toxicity continued for >2 weeks, one or both of the chemotherapeutic agents dose were reduced by 25%. Patients requiring doses to be withheld on two or more consecutive occasions were removed from study. Supportive treatment was administered as the patient's requirements. No radiotherapy was preplanned in this protocol.

Assessments

Physical and laboratory examinations were performed before each cycle. The objective tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria[14] every two cycles (every 6 weeks) using abdominal ultrasound, computed tomography or magnetic resonance imaging scans.

Toxicity analysis were carried out at the beginning of each cycle for each patient who received at least two cycle of the studied drugs and classified according to the Common Terminology Criteria for Adverse Events-National Cancer Institute, version 3.0.[15]

All patients were required to provide informed consent prior to study enrollment.

The primary study end point was assessment of the OS rate; secondary end points were assessment of the progression-free survival (PFS) rate, ORR and treatment toxicity.

Statistical analysis

The achieved response rates proportions were compared between the two treatment arms using the Chi-Square test. The overall response rate was defined as the sum of the partial response & stable disease.

Overall survival rate was calculated from the date of diagnosis to the date of death or last follow-up. Progression-free survival rate was calculated from the date of diagnosis to the date of disease progression. Both OS and PFS rate estimates were calculated using the Kaplan and Meier method,[16] the survival curves were compared between the two treatment arms using the log-rank test and *p*-values <0.05 were considered to be statistically significant.[17] For comparing toxicity rates, the Chi-Square test was used. Data were calculated using the Statistical Package for Social Sciences software (SPSS version 12, Chicago, IL).

3. Results

Patient characteristics

Thirty-nine pancreatic cancer patients, treated at Clinical Oncology Department, Tanta University Hospital, were enrolled in this trial from May 2008 to April 2012. Patient characteristics are shown in Table 1 and these were well balanced between the two arms. The majority of patients (69.2%) had an ECOG PS 2, and 64.1% of all patients had metastatic disease and the liver was the main site of distant metastasis.

Treatment

Table 2 shows, the mean number of total cycles of chemotherapy administered in this study were 4.7±1.8 cycles in Gem-Cap and 3.9±1.4 cycles in Gem-Ox arms. Patients received a median of 5 cycles (range, 2-10) and 4 cycles (range, 2-8) respectively. Treatment delays occurred in 47.6% of all cycles in the Gem-Cap arm and in 44.4% of all cycles in the Gem-Ox arm. In 35.9% of all treatment cycles, doses

had to be reduced mainly due to treatment-related toxicity. Whereas hematological toxicity was the main reason for dose reduction in the Gem-Cap arm (28.6%), non-hematological toxicity was the main cause for dose reduction in the Gem-Ox (27.8%) arm. The reasons for discontinuation of treatment were tumor progression, treatment-related toxic effects and patient refusal in both studied arms.

Table 1. Patient characteristics.

Characteristic	All patients n = 39 (%)	Gem-Cap n = 21 (%)	Gem-Ox n = 18 (%)	*p*
Age (years)				0.764
Median	61	60	62.5	
Mean	58.8	57.8	59.9	
Range	40-71	41-69	40-71	
Sex				0.656
Male	21 (53.8)	12 (57.1)	9 (50)	
Female	18 (46.2)	9 (42.9)	9 (50)	
ECOG PS				0.309
0 - 1	12 (30.8)	5 (23.8)	7 (38.9)	
2	27 (69.2)	16 (76.2)	11 (61.1)	
Primary tumor site				0.213
Head	29 (74.4)	15 (71.4)	14 (77.8)	
Body	6 (15.4)	2 (9.5)	4 (22.2)	
Tail	3 (7.7)	3 (14.3)	0 (0)	
Unknown	1 (2.5)	1 (4.8)	0 (0)	
Stage				0.303
Locally advanced	14 (35.9)	6 (28.6)	8 (44.4)	
Metastatic	25 (64.1)	15 (71.4)	10 (55.6)	
Site of metastasis				0.863
Liver	13 (33.3)	8 (38.1)	5 (27.8)	
Liver + Bone	5 (12.8)	3 (14.3)	2 (11.1)	
Liver + Lung	4 (10.3)	2 (9.5)	2 (11.1)	
Omentum/Peritoneum	3 (7.7)	2 (9.5)	1 (5.6)	
Baseline CA 19.9 (U/mL)				0.470
Median	570	500	649	
Mean	2752.8	2922.3	2555.2	
Range	4-35830	4-35830	7-23150	
Histology grade				0.857
G1	4 (10.2)	2 (9.5)	2 (11.1)	
G II	11 (28.2)	7 (33.3)	4 (22.2)	
G III/IV	15 (38.5)	7 (33.3)	8 (44.4)	
Missing/unknown	9 (23.1)	5 (23.8)	4 (22.2)	

Gem, gemcitabine; Cap, capecitabine; Ox, oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; CA 19-9, carbohydrate antigen 19-9; G, grade.

Response to treatment and survival results

At the time of final analysis, 35 (89.7%) deaths had occurred. Out of the total 39 patients, there were no complete response (CR), 23.8% in the Gem-Cap arm and 22.2% in the Gem-Ox arm had achieved partial response (PR) and 33.3% versus 44.4% had stable disease respectively. Progressive disease occurred in 42.9% of Gem-Cap arm and in 33.3% of the Gem-Ox arm. Patients assigned to Gem-Ox regimen had apparent but not significant improved overall response rate over Gem-Cap regimen (66.7% versus 57.1%, p=0.759). The median OS for Gem-Cap arm was 18 weeks and that for Gem-Ox arm was 17 weeks (p=0.717). The 1-year OS rates were 9.52% versus 11.11% respectively, (p=0.792). At the time of the analysis, 36/39 patients (92.3%) had an event relevant for determination of PFS. In addition, the median PFS for Gem-Cap arm was 15 weeks and that for Gem-Ox arm was 14 weeks (p=0.388). The 1-year PFS rates were 4.76% versus 8.33% respectively, (p=0.715), Table 3. Figures 1 & 2 showed that there were no statistical significant differences concerning with OS & PFS rates in both studied groups.

Toxicity results

Hematological toxicities in each treatment arm are summarized in Table 4. Myelosuppression of all grades was more frequent with the Gem-Cap arm in comparison with Gem-Ox arm. Grade 3/4 neutropenia was significantly represented in Gem-Cap arm in comparison with Gem-Ox arm, (28.6% vs. 5.6% respectively, p=0.023).

Non-hematological toxicity observations are shown in Table 4. Peripheral neuropathy in all grades was more frequent in Gem-Ox arm, p=<0.001, whereas there was an increase in hand-foot syndrome in all grades in Gem-Cap arm, p=0.001.

4. Discussion

Pancreatic adenocarcinoma is among the most challenging of solid malignancies to treat on account of its propensity for late presentation with inoperable disease, aggressive tumor biology and resistance to chemotherapy.[18, 19] Gemcitabine monotherapy had widely accepted as a cornerstone of therapy for patients with locally advanced or metastatic PC since Burris *et al*.,[20] reported their phase III trial results. Although it has shown clinical benefit, gemcitabine monotherapy has been associated with limited antitumor activity, with an ORR of 5% and median OS of 5.7 months. Also, Carmichael *et al*.,[21] reported a median survival duration following gemcitabine monotherapy of 6.3 months and the response rate was 11.0%. These poor outcomes clearly indicated the need for more effective treatment strategies for advanced pancreatic cancer.

Table 2. Chemotherapy cycles and its modifications during treatment.

Parameter	All patients (n = 39) No (%)	Gem-Cap (n = 21) No (%)	Gem-Ox (n = 18) No (%)	*p*
Total cycles	170	99	71	0.245
Mean	4.4±1.6	4.7±1.8	3.9±1.4	
Median	4	5	4	
Range	2-10	2-10	2-8	
Duration of treatment				0.381
Total (weeks)	464	264	200	
Mean	11.9±6	12.6±5.9	11.1±6.1	
Median	12	12	12	
Range	3-30	3-30	3-24	
Treatment delay				0.843
Yes	18 (46.2)	10 (47.6)	8 (44.4)	
No	21 (53.8)	11 (52.4)	10 (55.6)	
Dose reduction				0.096
No	25 (64.1)	13 (61.9)	12 (66.7)	
Hematological toxicity	7 (17.9)	6 (28.6)	1 (5.6)	
Non-hematological toxicity	7 (17.9)	2 (9.5)	5 (27.8)	
Treatment discontinuation				0.768
Yes	5 (12.8)	3 (14.3)	2 (11.1)	
No	34 (87.2)	18 (85.7)	16 (88.9)	

Table 3. Summary of efficacy results.

Parameter	All patients (n = 39) No (%)	Gem-Cap (n = 21) No (%)	Gem-Ox (n = 18) No (%)	*p*
Objective response rate				0.759
Complete response	0 (0)	0 (0)	0 (0)	
Partial response	9 (23)	5 (23.8)	4 (22.2)	
Stable disease	15 (38.5)	7 (33.3)	8 (44.4)	
Progressive disease	15 (38.5)	9 (42.9)	6 (33.3)	
Overall survival				0.717
Mean, weeks	21.7±13.5	22.1±13.4	21.4±14.4	
Median, weeks	18	18	17	
Range	5-57	8-57	5-55	
1-year OS rate	10.26%	9.52%	11.11%	0.792
Progression-free survival				0.388
Mean, weeks	18±13.8	17.5±12.9	18.6±15	
Median, weeks	14	15	14	
Range	3-54	4-52	3-54	
1-year PFS rate	6.41%	4.76%	8.33%	0.715

Table 4. Toxicity results.

Toxicity*	Gem-Cap (n = 21)		Gem-Ox (n = 18)		*p*
	Grade 1-2 No (%)	Grade 3-4 No (%)	Grade 1-2 No (%)	Grade 3-4 No (%)	
Neutropenia	15 (71.4)	6 (28.6)	13 (72.2)	1 (5.6)	0.023*
Thrombocytopenia	12 (57.1)	2 (9.5)	6 (33.3)	0 (0)	0.077
Anemia	14 (66.7)	5 (23.8)	9 (50)	1 (5.6)	0.028*
Hand-foot syndrome	10 (47.6)	1 (4.8)	0 (0)	0 (0)	0.001*
Peripheral neuropathy	0 (0)	0 (0)	9 (50)	2 (11.1)	<0.001*
Nausea	15 (71.4)	0 (0)	10 (55.6)	0 (0)	0.303
Vomiting	8 (38.1)	0 (0)	5 (27.8)	0 (0)	0.496
Diarrhea	6 (28.6)	3 (14.3)	4 (22.2)	3 (16.7)	0.899
Mucositis	6 (28.6)	1 (4.8)	4 (22.2)	1 (5.6)	0.901
Febrile neutropenia	0 (0)	3 (14.3)	0 (0)	0 (0)	0.095
*NCI–CTC, National Cancer Institute–Common Terminology Criteria for Adverse Events. Gem, gemcitabine; Cap, capecitabine; Ox, oxaliplatin.					

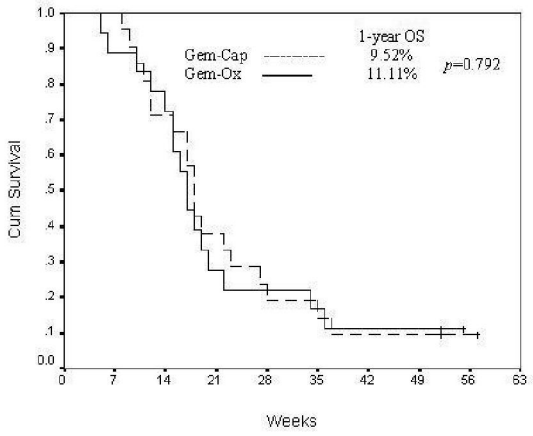

Fig 1. Overall survival by treatment arms.

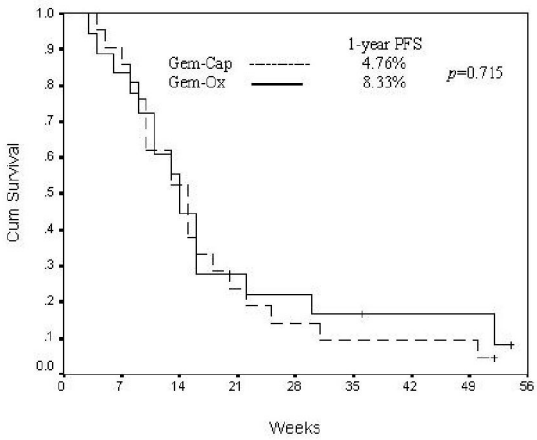

Fig 2. Progression-free survival by treatment arms.

The benefit of combining gemcitabine with a second cytotoxic agent still remains controversial in this disease. In the past decade, many randomized controlled trials evaluated gemcitabine combined with various cytotoxic or targeted agents to try to improve outcomes for patients with locally advanced or metastatic PC.[4]

Although some trials of combination therapies including gemcitabine and other cytotoxic agents, such as irinotecan and oxaliplatin, resulted in improved response rates over gemcitabine monotherapy, randomized phase III trials of these combinations have shown no significant survival benefits.[22, 24] Other phase III studies had reported negative results with no demonstration of improved efficacy for combinations of gemcitabine with the cytotoxic agents exatecan and pemetrexed, and the targeted agent tipifarnib. [24-26]

In general, the benefits of adding capecitabine or oxaliplatin to gemcitabine chemotherapy in locally advanced or metastatic PC are clear, with prolonged survival, improvement in disease control and improvement or stabilization of quality of life (QOL) as compared with gemcitabine monotherapy. [4]

This study is a prospective clinical trial that has compared two different chemotherapy doublets in the treatment of advanced PC. Patients assigned to Gem-Ox had a not significantly improved overall response rate over Gem-Cap (66.7% versus 57.1%, respectively; p=0.759). The 1-year OS rate was 9.52% in the Gem-Cap arm vs. 11.11% in the Gem-Ox arm, (p=0.792). The corresponding median survival time was 18 weeks vs. 17 weeks, respectively (p=0.717). The 1-year PFS rate was 4.76% in the Gem-Cap arm and 8.33% in the Gem-Ox arm, (p=0.715). Median PFS was estimated with 15 weeks and 14 weeks, respectively (p=0.388). Grade 3/4 hematological toxicities were more frequent in the Gem-Cap arm than Gem-Ox arm, p<0.05. Non-hematological toxicity presented with peripheral neuropathy was more frequent in Gem-Ox arm, p=<0.001, whereas hand-foot syndrome was more in Gem-Cap arm, p=0.001.

Boeck *et al.*,[27] in a multicenter, three-arm randomized phase II trial had randomly assigned 190

patients with advanced PC to receive Cap-Ox, Gem-Cap or Gem-Ox. The PFS rate after 3 months was 51% in the Cap-Ox arm, 64% in the Gem-Cap arm and 60% in the Gem-Ox arm. Median PFS was estimated with 4.2 months, 5.7 months and 3.9 months, respectively (p=0.67). Corresponding median survival times were: 8.1 months (Cap-Ox), 9.0 months (Gem-Cap) and 6.9 months (Gem-Ox) (p=0.56). Grade 3/4 hematological toxicities were more frequent in the two Gem-containing arms; grade 3/4 non-hematological toxicity rates did not exceed 15% in any arm.

The combination of gemcitabine with platinum was evaluated in eleven trials involving 2,379 patients. Three trials used oxaliplatin [28-30], and eight trials[31-38] used cisplatin combined with gemcitabine. In these trials, the gemcitabine/platinum combinations prolonged OS in nine trials, whereas no survival benefit was seen in two trials[31, 33].

Cunningham *et al*.,[12] showed a significant increase in median OS for the combination of Gem-Cap when compared to single-agent gemcitabine (7.4 vs. 6.0 months, p=0.026) with significantly improved ORR (19.1% vs. 12.4%; p=0.034) and PFS (p=0.004). On the basis of these results, he recommended that Gem-Cap should be considered one of the standard first-line options in locally advanced or metastatic PC. In this study, a 4-week regimen for capecitabine was used: capecitabine was given at a total dose of 1660 mg/m^2/day for 21 days every 4 weeks. In contrast, our trial used capecitabine 825 mg/m^2 twice daily po days 1–14 followed by a treatment free interval of seven days every 3 weeks. On the other hand, the Herrmann *et al.,*[11] (capecitabine 1300 mg/m^2/day for 2 weeks out of three used a 3-week regimen) failed to demonstrate a survival benefit for the Gem-Cap regimen (8.4 vs. 7.2 months, p=0.234) .

Recently, Choi *et al.,*[39] had studied 53 patients with advanced PC receiving 1,000 mg/m^2 gemcitabine intravenously on days 1, 8 and 15, and 830 mg/m^2 of oral capecitabine twice a day on days 1-21 of a 28-day cycle. The median time to progression and overall survival were 6.5 months and 10.0 months, respectively. Grade 3/4 toxicities included neutropenia (22%), anemia (8%), thrombocytopenia (6%) and hand-foot syndrome (10%).

5. Conclusion

Although our study had the limitation of being a single center study with a small sample of enrolled patients, our results can conclude that, the advanced pancreatic cancer is a fatal disease. The efficacy of the Gem-Ox regimen in the treatment of advanced PC seems to be similar to Gem-Cap regimen. However, the toxicity profile of the Gem-Ox regimen is different with significantly fewer hematological adverse events and the major side-effects were peripheral neuropathy whereas, the hand-foot syndrome being the main non-hematological toxicity in the Gem-Cap arm. Further multi-centers trials with large number of patient comparing different multi-agents' regimens with different dosage schedules for patients with advanced PC are warranted.

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