Gemcitabine plus Capecitabine Followed by Concurrent Chemoradiotherapy in Non-Metastatic Locally Advanced Pancreatic Cancer

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Abstract: Background: While it is proved that chemotherapy (CT) is the standard treatment modality for inoperable, non-metastatic, locally advanced pancreatic cancer (LAPC), concurrent radiotherapy (RT) with CT agents such as gemcitabine (GEM), capecitabine or fluorouracil is also an acceptable treatment option. **Purpose:** We aimed to assess the efficacy and tolerability of GEM plus capecitabine followed by concurrent GEM and three-dimensional conformal radiotherapy (3D-CRT) in non-metastatic LAPC. **Patients and Methods:** Thirty patients with inoperable, non-metastatic LAPC received induction CT consisted of 3 cycles of GEM (1000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15) and capecitabine (830 mg/m^2 orally, twice daily on days 1–21) in 28 day cycles followed with CRT consisted of gemcitabine 600 mg/m^2 weekly for 5 weeks concurrent with 3D-CRT for a total dose of 50.4 Gy in 28 fractions in 5.5 weeks and finally additional two CT cycles of gemcitabine at a dose of 1,000 mg/m^2 weekly for 3 weeks with 1 week rest between the 2 cycles. **Results:** After a median follow-up period of 10.5 months, 4 (13.3%) patients were alive. The median overall survival (OS) was 11.5 months with 43.3% 1-year OS rate and the median progression-free survival (PFS) was 8.3 months with 10% 1-year PFS rate. None of the patients had grade 4 toxicity with grade 3 nausea/vomiting, diarrhea, and fatigue was represented in 10%, 6.7%, and 6.7% of patients respectively. **Conclusions:** Gemcitabine plus capecitabine followed by concurrent GEM and 3D CRT for treatment of non-metastatic LAPC is active with acceptable tolerability and survival outcome.
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1. Introduction

Pancreatic cancer (PC) is the 12th common malignant disease and considered the 8th leading cause of cancer mortality that constitutes about 7% of cancer deaths worldwide [1,2].

Treatment options as surgery, radiation therapy (RT), chemotherapy (CT) and concurrent chemoradiotherapy (CRT) may extend overall survival (OS) and/or relieve symptoms in many patients. However, resection offers the only curative treatment. The overall one- and five-year survival rates for all stages of PC are 28% and 7% respectively [1].

Pancreatic cancer diagnosed localized with resectable availability in about 10% to 15% of patients and unresectable in 30% of patients. The treatment of unresectable locally advanced pancreatic cancer (LAPC) is a matter of challenge, however, either systemic CT or CRT are considered an accepted treatment modality with a median OS ranging from 8 to12 months [3-6].

The definition of LAPC is controversial; however, He et al. [7] had defined LAPC as vascular structures (superior mesenteric artery or vein, portal vein, hepatic artery or celiac axis) involvement.

The high rate of local failure especially with utilizing conventional external beam RT continues to be a major problem in the management of PC. With the integration of the modern RT techniques such as three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and stereotactic body radiation (SBRT), with its ability to decrease the radiation delivered to the normal surrounding structures, this problem can be solved [8].

Gemcitabine (GEM) as a potent radiosensitizer with its systemic efficacy in the treatment of PC has been investigated in many trials with improved OS and acceptable safety profile [6, 8-11].

Our study aimed to assess the efficacy and tolerability of concurrent use of GEM plus 3D-CRT for patients with non-metastatic inoperable LAPC after an induction phase of three cycles of GEM and capecitabine.

2. Patients and methods

This prospective phase II study included 30 patients with non-metastatic inoperable LAPC who were treated at Clinical Oncology Department, Tanta University Hospital throughout the period between January 2014 to July 2016 with a minimum follow-up period of 6 months. A written consent was obtained from all studied patients.

Eligibility criteria

Patients aged ≤18 years and not more than 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) from 0-2, non-metastatic locally advanced unresectable or operable but medically unfit for surgery with no lymph node involvement. All patients had adequate bone marrow, hepatic and renal functions with no prior CT or RT to the upper abdomen.

Exclusion criteria

Patients with histologic findings other than pancreatic invasive ductal adenocarcinoma, prior malignancy, medical conditions that would preclude protocol therapy, pregnant and lactating women were excluded.

Patient assessment

Patients were assessed by full personal, present, and past history; full clinical examination with evaluation of PS. Laboratory investigations included complete blood counts (CBC), renal and hepatic functions. The diagnosis was confirmed cytologically, histologically or radiologically by triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI) with elevated tumor markers; serum carbohydrate antigen 19-9 (CA19-9) and/or carcinoembryonic antigen (CEA). Radiological investigations to exclude metastasis include chest X-ray (or CT chest if there is suspicious lesion) and bone scan if indicated.

Treatment protocol

Induction Chemotherapy

Induction CT consisted of three cycles of GEM (1000 mg/m^2 over 30 minutes infusion on days 1, 8, and 15 of a 28-day cycle) and capecitabine (830 mg/m^2 orally, twice daily on days 1–21 of a 28-day cycle).

Chemoradiotherapy

Chemoradiotherapy consisted of GEM 600 mg/m^2 weekly for 5 weeks concurrent with RT. Radiotherapy was delivered by 3D-CRT modality. The patients underwent a treatment-planning computed tomography (CT) cuts obtained at 3- to 5-mm slice intervals for contouring the target volumes. Dose volume histograms were created for all treatment plans and all dosimetric data were transferred to 3-D radiotherapy planning system (RTPS) using Eclipse (Varian Medical Systems, Palo Alto, CA, USA). Gross tumor volume (GTV) was defined as the gross disease (primary tumor and enlarged regional lymph nodes), which was seen in the CT scan or MRI. Clinical target volume (CTV) was cover by 95% of isodose curves, inhomogeneity ranged from 95% to 105%, and doses to organs at risk were limited to their tolerances. The 3D-CRT was performed with photons using a linear accelerator 6 MV (Varian Medical Systems, Palo Alto, CA, USA) to a total dose of 50.4 Gy in 28 fractions in 5.5 weeks.

Then all patients had additional two CT cycles of gemcitabine at a dose of 1,000 mg/m^2 weekly for 3 weeks with 1 week rest between the 2 cycles.

All patients were reassessed for operability, with suitable patients taken to surgery. Those not suitable for surgery were followed-up and additional CT beyond the planned treatment protocol was not recommended unless disease progression was developed. Progression was defined according to radiological criteria, and an isolated rise in CA19-9 was not regarded as a criterion for progression. No specific regimen was recommended for treatment after progression.

Response assessment

Response assessment was done at least 1 month after the end of the treatment protocol using triphasic CT scan or MRI and tumor markers CA19-9 and CEA. Radiologic tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [12]. Complete remission (CR) was defined as complete disappearance of all target lesions without an occurrence of new lesions, a decrease in the level of tumor markers to the normal level which was maintained for four weeks. Partial remission (PR) was defined as a decrease in the sum of the longest lengths of all baseline target lesions ≥30% which was maintained for four weeks. Stable disease (SD) was defined as a decrease in the sum of the longest lengths of all baseline target lesions less than PR, or enlargement of the lesions without progression. Progressive disease (PD) was defined as an increase in the sum of the longest lengths of the detected smallest target lesion ≥20%, or occurrence of one or more new lesion sites.

Toxicity of treatment

Patients were clinically assessed with CBC and serum renal and liver profiles weekly during induction CT and CRT phases. At each visit, toxic effects from CT and RT were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [13]. Dose modifications for CT were made according to the grade of toxicity, the dose of CT were reduced by 25% in cases of ≥grade 3 toxicities. For recurrent grade 3 toxic effects, doses were reduced to 50%. If either the GEM or capecitabine dose was permanently discontinued, treatment with the remaining acceptable compound was continued according to the schedule. Chemoradiotherapy was discontinued if grade 3 or higher GIT toxic effects recurred more than once during CRT treatment.

Follow-up

Patients were followed-up every month by clinical examination, CBC, serum renal and liver functions and evaluation of toxic effects. Triphasic CT or MRI and tumor markers have done every 3 months

for the first year then every 6 months for the second year then annually.

Statistical analysis

The primary end point includes assessment of treatment response. The secondary end points include; evaluation of the OS, progression-free survival (PFS) rates and the safety profile of the treatment protocol.

Efficacy endpoints were analyzed according to the intention-to-treat principle as all patients who met the eligibility criteria were included in the analysis. Overall survival was calculated from the date of diagnosis to the date of death, regardless of cause or the last visit. Progression-free survival was defined as the time from the start of CT to the date of documented disease progression or last visit. Progression-free survival and OS were analyzed by the Kaplan-Meier method. Data were calculated using Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL) and $p < 0.05$ was regarded as significant.

3. Results

Patient and tumor characteristics

The median age of patients was 55 (range, 37-68) years with mean±SD age was 55.4 ±8.4 years and 70% presented with ECOG PS score <2. The most common site of the tumor was the head (73.3%). Positive LN metastases were represented in 66.7% of patients. The baseline serum CA19-9 level was measured in all patients before starting CT, 17 (56.7%) patients had elevated level more than 37 U/mL with the median baseline level was 286 (range, 11-1400) U/mL (Table 1).

Response rate

None of the patients had achieved CR, 4 (13.3%) patients had achieved PR, 20 (66.7%) patients had SD and 6 (20%) patients had PD (Table 2). The median duration of PR was 12.6 months. The median post-CRT CA 19-9 level was 87.5 (range, 15-1200) U/mL for all patients. Out of 17 (56.7%) patients who had elevated baseline CA 19-9 level more than 37 U/mL, 8 patients (47.1%) had achieved 50% reduction relative to the baseline value, 7 patients (41.2%) had stabilization (<50% reduction to <25% increase) and 2 patients (11.7%) had progression (>30% increase).

Survival outcome

The median follow-up time from treatment start was 10.5 (range 6-17.1) months. At the end of the follow-up period, 4 (13.3%) patients were alive while 26 (86.7%) patients had died. As regards the survival outcome for all patients, the median OS time was 11.5 (range, 6.6-18.1) months, mean±SD was 11.7±2.7 months and the 1-year OS rate was 43.3%. The median PFS time was 8.3 (range, 5.4-13.4) months, mean±SD was 8.8±2.1 months and the 1-year PFS rate was 10% (Table 2, Figure 1 & 2).

Distant failure had occurred in 5 (16.7%) patients, the liver was the main site of metastases (3 patients), followed by abdominal lymph node (1 patient) and the lung (1 patient).

At the end of study protocol surgical resection of the primary tumor had performed for two patients, these patients remained disease free at 36 and 41 weeks follow-up and both died from postoperative complications.

Table (1): Patient and tumor characteristics

Characteristic	No.	%
Age (years) Median 55, Range (37-68), Mean 55.4 ± 8.4		
≤ 55	15	50
> 55	15	50
Sex		
Male	21	70
Female	9	30
Performance status		
0	6	20
1	15	50
2	9	30
Site of tumor		
Head	22	73.3
Body & tail	8	26.7
Tumor grade		
Low	0	0
Moderate	8	26.7
High	9	30
Unknown	13	43.3
Nodal status		
Positive	20	66.7
Negative	10	33.3
Baseline CA19.9 (U/mL): Median 286, Range (11-1400), Mean ±SD 385.3±431.3		

Table (2): Summary of efficacy results.

Response rate	No.	%
CR	0	0
PR	4	13.3
SD	20	66.7
PD	6	20.0
Overall survival		
Median, months	11.5	
Range, months	6.6-18.1	
One year OS rate	43.3%	
95% CI	9.89-13.11	
Progression-free survival		
Median, months	8.3	
Range, months	5.4-13.4	
One year PFS rate	10%	
95% CI	7.63-8.97	

Toxicity of treatment

Patients were evaluated for adverse events during the induction CT and CRT phases (Table 3). None of the patients developed grade 4 toxicity and no treatment-related death had been recorded. During the induction phase, grade 3 thrombocytopenia and anemia were represented in 6.7% and 3.3% of patients respectively. Grade 3 nausea/vomiting, diarrhea, and fatigue was represented in 10%, 6.7%, and 6.7% of patients respectively.

Four patients had required CT dose reduction of induction regimen by 25% of the planned dose due to non-hematological toxicity. The median time from the end of induction CT to the start of CRT was 2 (range 1-3) weeks.

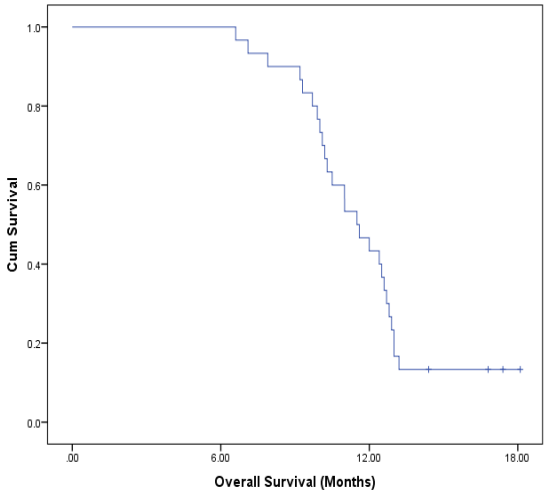

Figure (1): OS of all treated patients

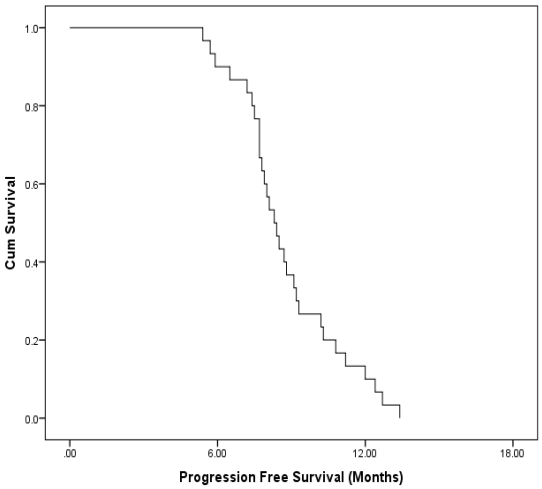

Figure (2): PFS of all treated patients

Table (3): Toxicity of treatment.

Toxicity	Induction CT (n=30)			CRT (n=30)		
	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)
Anemia	4 (13.3%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0%)
Leukopenia	2 (6.7%)	2 (6.7%)	0 (0%)	2 (6.7%)	1 (3.3%)	1 (3.3%)
Thrombocytopenia	6 (20%)	2 (6.7%)	2 (6.7%)	3 (10%)	1 (3.3%)	0 (0%)
Infection/febrile neutropaenia	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)
Nausea/Vomiting	8 (26.7%)	3 (10%)	3 (10%)	4 (13.3%)	3 (10%)	2 (6.7%)
Diarrhea	2 (6.7%)	0 (0%)	2 (6.7%)	1 (3.3%)	2 (6.7%)	2 (6.7%)
Fatigue	6 (20%)	3 (30%)	2 (6.7%)	3 (10%)	3 (10%)	1 (3.3%)
Anorexia	3 (10%)	1 (3.3%)	0 (0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)
Constipation	4 (13.3%)	1 (3.3%)	1 (3.3%)	4 (13.3%)	0 (0%)	0 (0%)
Neuropathy	2 (6.7%)	2 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0%)
Hand-foot syndrome	1 (3.3%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)

During the CRT phase, the grade 3 adverse events were leukopenia (3.3%), nausea/vomiting and diarrhea (6.7%, for both). Three (10%) patients required CT dose reduction of GEM by 25% of the planned dose and only 1 patient discontinued GEM as he developed grade 3 neutropenic fever. About 85% of treatment toxicities started to appear after the 3rd week of therapy.

Only two patients required discontinuation of RT after 2700 & 4140 cGy due to grade 3 non-hematological toxicity. In the remaining patients, the RT program was not modified; with median time for CRT was 38 (range 24-48) days.

4. Discussion

The contribution of RT to the improvement of survival and quality of life of inoperable LAPC is a controversial issue as many patients die from the rapidly emerging metastatic disease. Survival of

patients with LAPC, who are treated with CT alone, ranges from 9.9 to 10.3 months [14, 15].

Trials that have assessed CRT started with induction CT aiming at the early initiation of effective systemic therapy followed by intensified consolidation CRT for patients not developing metastatic disease for optimal local tumor control and sometimes tumor downstaging with increased the probability of radical resection with reported OS rates ranged from 14 to 19 months [16-23].

Gemcitabine is a documented radiosensitizer but elevated toxicity had been recorded with higher doses of GEM in combination with RT. The optimum dose of GEM given concurrently with RT is undefined. While we used GEM at a dose 600 mg/m^2 once per week concurrent with RT, phase I–II clinical trials utilized GEM weekly in doses ranged from 250 mg/m^2 to 1000 mg/m^2 [16]. Loehrer et al. [6] in a phase III trial had randomly assigned 71 PC patients to receive GEM either alone or as a radiosensitizer at a dose of 600 mg/m^2. Survival outcome was 11.1 vs. 9.2 months in CRT and CT alone groups (p=0.017) with increased high-grade toxicities in CRT group (41% vs. 9%) respectively.

Trials used GEM in a full-dose combined with radical doses of RT has been reported with promising results and acceptable toxicities. However, these studies were done in a small number of centers [24, 25].

Two prospective trials were designed to compare the established 5-fluorouracil (5-FU) and RT versus GEM alone or combined with RT for LAPC. In a phase III trial reported with Chauffert et al. [26] there was an improvement of the survival outcome for patients treated with GEM alone vs. combined RT with 5-FU (13.0 vs. 8.6 months). The Taipei trial reported improved OS (14.5 months) with combined GEM and RT versus 6.7 months with combined 5-FU and radiation [10].

The idea about the benefit of starting with the induction phase aiming to exclude the non-responsive and metastatic cases before the CRT phase which is reflected on the end result of the outcome as regards the OS and PFS. This theory is confirmed by Gillmore et al. [21] in a retrospective multicentre study of 48 patients with pathologically confirmed LAPC treated with either CRT from the start or starting with induction CT in four oncology centers in the United Kingdom. The disease control rate was 73.4% vs 81.3% and the median OS was 13 vs. 17 months respectively. The same idea was supported in a published non-randomized series of 181 patients who were treated with GEM-based CT for 3 months, and those with stable disease were treated with CRT or CT alone. The median OS was significantly longer in patients received CRT than those received CT alone (15 months vs. 11.7 months respectively). This shows a probable benefit of CRT in patients who have achieved stable disease with induction CT [17].

The treatment protocol applied in this study resulted in 13.3% overall response rate, median OS was 11.5 (range, 6.6-18.1) months and the 1-year OS rate was 43.3%. The median PFS was 8.3 (range, 5.4-13.4) months and the 1-year PFS rate was 10%.

The results of our study were lower than that reported in a multicentric study done by Mukherjee et al. [16] where the 1-year OS rate was 64.2% with a median survival time was 13.4 months, the median PFS time was 10.4 months and the overall response rate was 19%. Huang et al. [27] had compared concurrent GEM at a dose of 1000 mg/m^2 weekly with involved-field RT with or without erlotinib versus capecitabine or infusional 5-FU concurrent with standard field RT in the treatment of 93 patients with LAPC. The median OS time was 12.5 months and the 1-year OS rate was 51% in the GEM-RT arm.

Shibuya et al. [28] had investigated the outcome of weekly GEM in a dose of 250 mg/m^2 given concurrently with 54 Gy RT per 30 fractions. Radiological PR was observed in 23%, SD was noted in 52% and the disease was progressed in 25% of patients. The 1-year OS rate was 74% with median survival time 16.6 months. Concomitant GEM plus RT was also studied by Cardenes et al. [29] where 28 LAPC patients received concurrent RT (50.4 Gy) with weekly GEM in a dose of 600 mg/m^2. Twenty-one percent of patients had achieved radiologic PR, the 1-year OS rate was 30% with median survival time 10.3 months and the median time to progression (TTP) was 6 months.

On the other hand, Hudson et al. [30] reported that, out of 69 patients with LAPC, 43 patients were considered for induction CT followed by CRT and 16 patients received CRT from the start. The median OS for patients receiving primary CT was 9.2 months and was 15.3 months for patients who received CRT.

In our study, as regards the toxicity assessment, grade 3 hematological toxicity was recorded in 10% and 6.7% of patients in the induction CT and CRT phases respectively while grade 3 nonhematological toxicity was recorded in 33.3% and 20% of patients in the induction CT and CRT phases respectively. Mukherjee et al. [16] recorded 18% and 26% grade 3–4 hematological and nonhematological toxic effects respectively during CRT phase and concluded that after induction of CT, RT concurrent with capecitabine-based regimen might be preferable than concurrent RT with a GEM-based regimen for LAPC.

While Elzahi et al. [31] recorded 37.5% grade 3 nonhematological toxic effects during CRT phase, Loehrer et al. [6] compared GEM alone and GEM with RT and concluded that, the benefit of adding RT to CT came at the cost of increased GIT toxicity as grade 3

GIT toxicity was 23% and 38% in GEM and GEM-RT arms respectively. However, in comparison to other studies of CRT using other agents than GEM, our protocol seems to be safer and less toxic. For examples, Oberic et al. [32] studied 5-FU and docetaxel with RT in 40 patients with LAPC and recorded that 20 (60%) patients experienced grade 3-4 toxicities during CRT treatment. Also, Saif et al. [33] studied capecitabine concurrent with RT in 82 patients with LAPC and recorded 66 (80%) patients experienced grade 3 or greater toxicity with 3 treatment-related deaths. On the other hand, Huang et al. [27] reported that the rates of acute and late grade 3–5 GIT toxicities were not significantly different between the GEM- RT and 5-FU-RT groups.

Some studies suggest that addition of other agents to GEM during the RT not only leads to more toxicity with no benefit but also to worse results as regards the response, OS, and PFS rates. Mamon et al. [34] had studied 78 LAPC patients treated with concurrent RT (50.4 Gy) and 200 mg/m^2 GEM weekly with infusional 5-FU (200 mg/m^2/5 days/week). Patients received 1000 mg/m^2 GEM weekly after a 3-week break on days 1, 8, and 15, cycles repeated every 4 weeks for 4 cycles. The 1-year OS was 51% with median OS time was 12.2 months and TTP was 10 months.

In another study done by Arnoletti et al. [35], 16 patients with non-metastatic, LAPC were treated with GEM given concurrently with cetuximab and RT (50.4 Gy). The most frequent grade 3 toxicity was thrombocytopenia (73%) and hyperkalemia (68%). The most grade 4 toxicity was perforated duodenum (19%) and pulmonary embolism (12.5%). The OS was 10.5 months.

In conclusions, GEM plus capecitabine followed by concurrent GEM and 3D CRT for treatment of non-metastatic LAPC is active with acceptable tolerability and survival outcome.

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