Abstract

**Aim**: The purpose of this study was to compare efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine-cisplatin as first-line therapy in patients with pancreatic cancer.

**Method**: Pancreaticobiliary cancer patients who had Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating greater severity of illness) were evaluated to receive FOLFI RINOX or gemcitabine plus cisplatin. The primary endpoints were progression free and overall survival time. Safety analysis was also evaluated as secondary measures.

**Results**: There were 32 patients in the FOLFIRINOX group and 36 patients in the gemcitabine-cisplatin group. The median overall survival was 18.1 months (7.5-28.7) in the FOLFIRINOX group as compared with 9.7 months (6.5-13) in the gemcitabine-cisplatin group (p:0.009). Median progression-free survival was 16.2 months (9-23.4) in the FOLFIRINOX group and 6.9 months (6.1-7.6) in the gemcitabine-cisplatin group (p:0.001).

**Conclusion**: FOLFIRINOX is an option for the first-line treatment of patients with pancreatic cancer and good performance status.

**Keywords**: Pancreatic cancer, Folfirinox, Gemcitabine-cisplatin, Effectiveness, Side effect
**Introduction**

Pancreatic cancer (PC) is one of the leading cause of cancer mortality in the world. Although new therapeutic strategies have been developed; unfortunately the overall 5-years survival is approximate 5%[1] and the fourth leading cause of deaths caused by cancer in the world [2]. Several treatment modalities including surgery, chemotherapy, molecular and biological targeted therapy are used for the treatment of pancreatic cancer treatment [3]. Among these modalities, chemotherapy is the treatment option for treating advanced or metastatic PC [4]. Without chemotherapy life span of patients is reported to be only 2-4 months [5].

A single agent or certain combination chemotherapy regimens have been shown to prolong survival with tolerable toxicity profiles. As single-agent gemcitabine has been used for local, advanced and metastatic PC. It has good tolerability and clinically response rate [6, 7]. But despite this potential, PC still had a poor prognosis, thus new chemotherapy regimens have emerged. Since 2011 FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil combination) regimen has been increasingly used and getting gold standard in the treatment of pancreatic cancer. In several studies, the overall survivals have ranged from 10 to 32.7 months and progression-free survivals have ranged from 3 to 20 months [8]. On the other hand, side effects including neutropenia, diarrhoea, neuropathy and thrombocytopenia have been seen more often than isolated gemcitabine regimen.

Gemcitabine based regimen is one of the options for treatment of unresectable and metastatic pancreatic cancer. The efficacy and toxicity of this regimens have been studied in several studies. In one of these studies, gemcitabine-cisplatin (Gem-Cis) regimen has better survival results with respect to other gemcitabine combination, these results statistically aren't meaningful though [9]. In toxicity perspective, Gem-cis combination had unfavourable results(10) But in these studies, gem-cis combination has not been compared to FOLFIRINOX in terms of efficacy and safety directly.

In this study, we retrospectively evaluated the safety and efficacy of FOLFIRINOX and Gem-Cis combination in unresectable and metastatic pancreatic cancer patients.

**Material and Method**

Pancreaticobiliary cancer patients were diagnosed and treated in Gazi University Oncology Department between January 2010 and July 2017 were retrospectively
evaluated. Patients medical records were investigated and only with either
FOLFIRINOX or Gemcitabine-Cisplatin given were selected. Patients who didn't come
to control, have missing variables and died before first control were excluded. Locally
advanced or metastatic pancreatic cancer was included. Patients who had Eastern
Cooperative Oncology Group performance status score of 0 or 1 were chosen. The
primary end-point was survival time at the end of the study. Safety analysis was the
secondary end-point. The study was approved by the local ethic committee (approval
number:2017/147)

Oxaliplatin, 85 mg per square meter of the body-surface area; irinotecan, 180
mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per
square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour
continuous infusion, every 2 weeks were given in FOLFIRONOX regimen.
Gemcitabine at a dose of 1000 mg per square meter weekly for 1. and 2. week, cisplatin
at a dose of 100 mg per square meter weekly for 1. week, every 3 weeks were given in
Gemcitabine-Cisplatin combination regimen

Tumour response was evaluated at every 10-12 weeks by computed
tomography. In some cases, magnetic resonance imaging (MRI) and positron emission
tomography were also used. Tumour response was assessed using computed
tomography and graded according to the Response Evaluation Criteria in Solid Tumors
(RECIST) version 1.1[10]. Progression-free survival was defined as starting from the
assignment in a clinical trial to disease progression or death from any cause. Overall
survival was starting at the assignment, to the date of death due to any cause, or to the
date of censoring at the last time the subject was known to be alive in intention-to-treat
populations.

Statistical analysis

Patients demographic data, tumour stage and histopathological characteristics,
chemotherapy-related documented side effects were compared. Continuous data were
presented as mean ± SD. Categorical variables were provided as percentages. In
univariate analysis, Student’s t-test / Mann–Whitney test were used to compare
continuous variables while chi-square and Fisher’s exact test were used for categorical
variables. Kaplan Meier Survival Analysis was used for progression-free survival time
and overall survival time estimation. Univariate and multivariate analyses were
performed using Cox proportional hazards regression to investigate prognostic factors
for progression-free survival (PFS) and overall survival (OS). The variables which
showed potential relation with PFS and OS in the univariate analyses (p< 0.2) were further evaluated in the multivariate analyses. A two-sided P-value of 0.05 or less was considered statistically significant. SPSS 15 (Statistical Package for the Social Sciences) is used for statistical analysis.

**Results**

**Baseline Characteristics**

Pancreaticobiliary cancer was diagnosed in 169 patients. Either FOLFIRINOX or Gem-Cis therapy given patients number was 105. Totally 68 patients were eligible for this study, remaining 37 patients had missing baseline information or did not attend first control. Demographic data and baseline characteristics were shown in table 1. 32 patients had FOLFIRINOX and 36 patients had Gem-Cis chemotherapy regimen. Median follow-up time 13.6 months for FOLFIRINOX group (min/maximum 4.4 and 45.3 respectively) and for Gem-Cis groups it was 10.9 months (min/maximum 5.13-and 46.4 respectively). Stage 4 patients were 20 (62.5%) in FOLFIRINOX group and 22 patients (61.1%) in gem-cis group. Mean 8.2 cycle (4-17) FOLFIRINOX and 5.9 (3-14) cycle Gem-Cis was given (p:0.022). Mean age in the FOLFIRINOX group was 50.2 whereas in Gem-Cis group it was 58.30 (p:0.27). ECOG performance status was also similar in both groups as shown in table 1.

Major pathologic tumour type in both treatment groups was adenocarcinoma of the pancreas 30 (93.8%) versus 34 (94.4%) as respectively. Tumour localizations were also similar for both groups, head of the pancreas were the most frequently seen localization then corpus and tale came second and third respectively. Stage 4 patients have outnumbered in treatment arms and liver was the primary site for metastasis (Table 1).

**Efficacy**

Treatment responses and efficacy data were shown below in figure 1-2. At any time 65.6% of FOLFIRINOX patient and 86.1% of Gem-Cis patients had progression. Median progression-free survival (PFS) time for FOLFIRINOX was 16.2 months (9-23.4) whereas for Gem-Cis was 6.9 months (6.1-7.6) (p:0.001) (figure 1) . In subgroup analysis patients with metastasis were 20 and their median PFS was 16.2 months (9.2-23.2) on the other hand in Gem-Cis group there were 22 patients and PFS were 6.4 months (5.4-7.4) (p:<0.05). The difference was also obvious in the locally advanced
group; for FOLFIRINOX group 12 months (3.2-29.3) versus for Gem-Cis group 7.1 months (5.9-8.4) (p<0.05).

At the end of the study in FOLFIRINOX group 12 patients (37.5%) and in Gem-Cis group, 4 patients (11.1%) were still alive. Median overall survival (OS) time for FOLFIRINOX group was 18.1 months (7.5-28.7) and for Gem-Cis group was 9.7 months (6.5-13) (p=0.009) (figure 2). In subgroup analysis for metastatic group median OS in FOLFIRINOX group was 11.3 months (5.5-17.4) versus in Gem-Cis group was 10.3 months (5.5-15.1) (p=0.34). Whereas in the locally advanced group it was 25.4 months (22.7-53) and 7.4 months (6-9.7) as respectively (p=0.005).

Safety Profile

Safety analysis was available in 32 patients of FOLFIRINOX and 36 patients of Gem-Cis group. They were shown in table 2. Grade 3-4 neutropenia was more frequently seen in FOLFIRINOX group (56 % vs. 39% p=0.224), grade 3-4 thrombocytopenia was encountered more often in Gem-Cis group (9.4% vs. 27.8% p=0.016). Anaemia frequency in any grade was similar for both treatment groups. This was also same for liver and kidney function test results. FOLFIRINOX group had more liver and kidney dysfunction but it did not statistically significant compared to Gem-Cis group.

Patient having diarrhoea which was resulted in hospitalization was 3 in the FOLFIRINOX group, whereas it was only 1 patient in Gem-Cis group (p=0.52). There weren't any patients having a neurotoxicity in FOLFIRINOX group; however, there were 5 patients in Gem-Cis group, who suffered from severe neuropathic complaints and had abnormal EMG consistent with neuropathic dysfunction.

As a result of side effects, the number of patients having chemotherapy dose reduction was 4 in the FOLFIRINOX group and 5 in the Gem-Cis group. On the other hand treatment was terminated in 2 patients of FOLFIRINOX and 5 patients Gem-Cis group (p>0.05)

Discussion

Pancreatic cancer is still far from being satisfactory in terms of prognosis, especially for metastatic disease. Several chemotherapy protocols have been used and gemcitabine-based protocols historically have had an important role in treatment. By combining with other chemotherapeutics, it was thought that better response rates could be achieved. However, as in this study shows, the FOLFIRINOX regimen was superior
to the gemcitabine-cisplatin combination. The safety analysis of both treatment regimen was similar, thus FOLFIRINOX must be used as a first-line in the treatment of pancreaticobiliary cancer.

The gemcitabine - cisplatin combination was previously compared to isolated gemcitabine treatment in a phase 3 study. In combination regimen, progression-free survival and the overall response rate was better but overall survival rate and safety profile were not different between groups [11]. Contrarily this combination resulted in more haematological side effects in another study [12]. In a review comparing gemcitabine-based regimen, in subgroup analysis gemcitabine-cisplatin combination had an advantage for survival but it didn't reach statistical significance [9]. For the tumour response rate, gem-cis regimen had a better partial and overall response rate. Also, disease progression rate was worse in isolated gemcitabine group [12-15]. On the other hand, the FOLFIRINOX regimen had a strong impact on overall survival, progression-free survival compared to isolated-gemcitabine treatment [16-18].

In literature, there isn't any study directly comparing these two regimens to our knowledge. FOLFIRINOX protocol had better survival ratios but also more side effects as compared to isolated gemcitabine protocol. In this study, FOLFIFOX group had more neutropenia, diarrhoea thrombocytopenia and sensorial neuropathy [18]. In a meta-analysis comparing all chemotherapy protocols used in pancreatic cancer were evaluated in terms of toxicity and efficacy. Although there weren't any direct comparison, FOLFIRINOX had the best short-and long-term efficacy among the 12 chemotherapy regimens. On the other hand FOLFIRINOX. Gemcitabine + Pemetrexed regimens had a relatively higher incidence of toxicity than other regimens [19]. Another meta-analysis comparing toxicity profiles of these regimen, Gemcitabine + Cisplatin and FOLFIRINOX regimens exhibited the highest incidence rates of neutropenia [20].

In this study, severe neutropenia and diarrhoea were more frequently seen in the FOLFIRINOX group but it didn't reach statistical significance. Contrary, severe thrombocytopenia was more prevalent in the gemcitabine group (p:0.069). All patients with the diagnosis of neuropathy belonged to the gemcitabine group. It may be as a result of shorter follow up period for FOLFIRINOX group and also this should be cautiously interpreted with the consideration of additive cisplatin toxicity that might impact on these increased side effects.
Survival ratios were consistent with the literature. In a review, 11 studies were included and resulted in mean overall survival 24.2 months (10-32) and mean progression-free survival of 15 months (3-20) [8]. Also, FOLFIRINOX protocol survival ratios were significantly better than gemcitabine group in locally advanced patients. But the difference diminished in the metastatic group. Increased tumour burden of the disease that rendered the difference irrelevant might be the explanation.

This study has some limitations, it is retrospective, single-center and nonrandomized this may cause selection bias and confound. Also, safety profiles data in our analysis may have missed due to a lack of identification of adverse events as a result of being retrospective data. Moreover, our study population was homogeneous as most patients had good PS, which might affect the tolerability of the regimens.

In conclusion, FOLFIRINOX is a better option for locally advanced and metastatic pancreaticobiliary carcinoma treatment than gemcitabine-cisplatin combination and can be used as first-line chemotherapy at the real-world setting. Toxicity profile should be kept in mind, especially haematological and gastrointestinal toxicity, which can cause severe morbidity and mortality and be managed by decreasing or modifying drug dosage.

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>Gem-Cis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient (n)</td>
<td>32</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Female (n) (%)</td>
<td>14 (43)</td>
<td>19 (52)</td>
<td>0.309</td>
</tr>
<tr>
<td>Age (mean)(std)</td>
<td>57.2±5.22</td>
<td>58.3±4.89</td>
<td>0.456</td>
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<tr>
<td>ECOG (n) (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>11 (34)</td>
<td>13 (36)</td>
<td>0.227</td>
</tr>
<tr>
<td>1</td>
<td>21 (67)</td>
<td>23 (64)</td>
<td></td>
</tr>
<tr>
<td>DM (n) (%)</td>
<td>23 (71.9)</td>
<td>25 (69.4)</td>
<td>0.520</td>
</tr>
<tr>
<td>HT (n) (%)</td>
<td>28 (87.5)</td>
<td>24 (66.6)</td>
<td>0.140</td>
</tr>
<tr>
<td>Smoking (n) (%)</td>
<td>9 (28.1)</td>
<td>14 (38.9)</td>
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</tr>
<tr>
<td>Alcohol (n) (%)</td>
<td>2 (6.3)</td>
<td>3 (8.3)</td>
<td>0.557</td>
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<tr>
<td>Adenocancer (n) (%)</td>
<td>30 (93.8)</td>
<td>34 (94.4)</td>
<td>0.258</td>
</tr>
<tr>
<td>Signet Ring Cell (n) (%)</td>
<td>0</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic (n) (%)</td>
<td>0</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine (n) (%)</td>
<td>2 (6.2)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1 Demographic and disease characteristics of study population; ECOG: DM diabetes mellitus, HT: hypertension*
### Table 2: Safety profile of treatment regimens

<table>
<thead>
<tr>
<th>Tumour localization (n) (%)</th>
<th>FOLFIRINOX (n:32)</th>
<th>Gem-Cis (n:36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>21 (65.6)</td>
<td>20 (55.6)</td>
<td>0.260</td>
</tr>
<tr>
<td>Corpus</td>
<td>3 (9.4)</td>
<td>8 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>3 (9.4)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Duodenum- biliary tract</td>
<td>5 (15.6)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Stage (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2B-3 (Local Advanced)</td>
<td>12 (37.5)</td>
<td>14 (38.9)</td>
<td>0.553</td>
</tr>
<tr>
<td>Stage 4 (Metastatic)</td>
<td>20 (62.5)</td>
<td>22 (61.1)</td>
<td></td>
</tr>
<tr>
<td>Anemia (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>24 (75)</td>
<td>30 (83.3)</td>
<td>0.658</td>
</tr>
<tr>
<td>Severe</td>
<td>20 (62.5)</td>
<td>26 (72.2)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>4 (12.5)</td>
<td>4 (11.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Neutropenia (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>26 (81.25)</td>
<td>26 (72.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (25.0)</td>
<td>12 (33.3)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>18 (56.25)</td>
<td>14 (38.9)</td>
<td>0.224</td>
</tr>
<tr>
<td>Thrombocytopenia (n) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>19 (59.4)</td>
<td>17 (47.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Severe</td>
<td>16 (50.0)</td>
<td>7 (19.4)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>3 (9.4)</td>
<td>10 (27.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Liver function tests abn. (n) (%)</td>
<td>11 (34.30)</td>
<td>11(30.4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Renal function tests abn. (n) (%)</td>
<td>12 (37.5)</td>
<td>6 (16.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diarhea (n) (%)</td>
<td>3 (9.3)</td>
<td>1 (2.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Neuropathy (n) (%)</td>
<td>-</td>
<td>5(13.8)</td>
<td>-</td>
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</table>
Figure 1: Progression free survival of treatment groups.

Figure 2: Overall survival of treatment groups.

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