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The Reallife Comparison of FOLFIRINOX vs Gemcitabine Platinum Combination as a First-Line Treatment in Patients with Pancreatic Carcinoma

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ABSTRACT Objective: The vast majority of pancreatic carcinoma patients have unresectable or metastatic disease at the time of diagnosis. Therefore, the 5-year survival rate is approximately 10%. FOLFIRINOX is used as a standard first-line therapy in patients with good performance status and as a single agent for patients with poor performance. Our study aimed to compare the combination of FOLFIRINOX and gemcitabine plus platinum-based therapy in the first-line treatment of unresectable metastatic pancreatic cancer. **Material and Methods:** Patients diagnosed with locally unresectable and metastatic pancreatic cancer at Gazi University Hospital between 01.2012 and 01.2020 were retrospectively screened. **Results:** The progression-free survival (PFS) and overall survival (OS) did not significantly differ between the FOLFIRINOX and gemcitabine plus platinum groups (p=0.22 and p=0.192, respectively). Moreover, there was no significant difference in the disease control rate (DCR) between the FOLFIRINOX and gemcitabine plus platinum groups (78.6% vs. 73.1%, respectively; p=0.64). The incidence of neutropenia fever and all-grade mucositis, diarrhea, and neuropathy was significantly greater in the FOLFIRINOX group (p=0.036, p=0.021, p=0.009, p=0.021, respectively). However, there were no significant differences in the incidence of Grade 3-4 side effects, interruption due to side effects, or treatment discontinuation (p=0.60, p=0.33, p=0.8, respectively). **Conclusion:** Although there was an improvement in OS of 4 months in favor of FOLFIRINOX, no statistically significant difference was found in the median OS, PFS, or DCR between patients treated with gemcitabine and patients treated with platinum agents.

Keywords: Pancreatic cancer; matastatic; overall survival; adverse events; chemotherapy; performance status

The majority of patients with pancreatic cancer (PCa) (80-85%) are diagnosed with a disease that cannot be surgically removed or has spread to other parts of the body. Despite improvements in treatment methods, the five-year survival rate for patients with advanced pancreatic adenocarcinoma remains at 10%.[1,2] Until the early 2000s, the treatment for PCa involved the use of a single agent, either 5-fluorouracil (5-FU) or gemcitabine (GEM).[3] Low response rates to these treatments necessitated the exploration of new therapeutic options. In a 2002 Phase II study, the evaluation of adding oxaliplatin to gemcitabine (GEMOX) led to an increase in the response rate from 17.3% to 26.8%.[3-5] In 2006, the introduction of cisplatin to the gemcitabine regimen (GEMCIS) resulted in numerically extended overall survival (OS) and progression-free survival (PFS), although these increases were not statistically significant. Additionally, the disease control rate (DCR) was observed to be greater in the combination treatment group.[6]

In 2005, the initial use of the FOLFIRINOX chemotherapy regimen (oxaliplatin 85 mg/m^2 over 2 hours, followed by irinotecan 180 mg/m^2 over 90 min and leucovorin 400 mg/m^2 over 2 hours, followed by FU 400 mg/m^2 bolus and 2,400 mg/m^2 continuous infusion over 46 hours) was assessed in a Phase II

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study, and its effectiveness was confirmed.[7] A subsequent Phase III study of the French trial comparing FOLFIRINOX and gemcitabine alone found a significant 4.3-month improvement in the primary endpoint of OS in the FOLFIRINOX group.[8]

FOLFIRINOX is still one of the standard first-line treatment options for unresectable metastatic PCa. All phase studies demonstrating the success of FOLFIRINOX treatment include patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0-1.[9] However, in clinical practice, unresectable patients with metastatic disease may have worse performance scores since guidelines still indicate that the single agent gemcitabine is an option for patients with an ECOG score >1.

To the best of our knowledge, there are no prospective studies in the literature evaluating the effect of FOLFIRINOX and gemcitabine combination therapys head-to-head. In addition, the number of retrospective studies comparing these treatment regimens is quite limited. Considering the effectiveness of platinum therapy in treating PCa, a comparison of FOLFIRINOX and gemcitabine combination therapy is critical to determine whether similar efficacy can be achieved with less toxicity.[10] Our study aimed to evaluate the effectiveness of FOLFIRINOX and gemcitabine/platinum combination therapies on survival without excluding fragile patients with unresectable metastatic PCa.

MATERIAL AND METHODS

Patients diagnosed with locally unresectable and metastatic PCa at Gazi University Hospital between 01.2012 and 01.2020 were retrospectively screened. Our study was approved by the Gazi University Ethics Committee with the approval number E-77082166-604.01.02-23576 on January 26, 2021. The study was designed and implemented in accordance with the principles of the Helsinki Declaration. The inclusion criterion for the present study was a diagnosis >18 years old and an ECOG performance score ≤2. Patients who received at least one course of chemotherapy and survived for at least four weeks after the diagnosis of unresectable metastatic disease were included in the study. Patients whose chemotherapy-related side effect data could not be obtained and who were likely to receive local treatment after first-line treatment were excluded from the study.

The patients received gemcitabine+cisplatin (GEMCIS), gemcitabine+oxaliplatin (GEMOX) or 5-FU+oxaliplatin+irinotecan (FOLFIRINOX) as chemotherapy regimens. GEMOX and GEMCIS recipients were evaluated together as a gemcitabine/platinum group. The initial dose administration schedule for chemotherapy treatment is given in the Appendix 1.

Patient treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors. The DCR was defined as the percentage of patients with unresectable or metastatic cancer who achieved a complete response (CR), partial response (PR) or stable disease (SD) with anticancer agents. The overall response rate (ORR) was defined as the proportion of patients who achieved a partial or CR to therapy. OS was defined as the time from diagnosis of unresectable or metastatic disease to death or last control. PFS was defined as the time from the diagnosis of unresectable or metastatic disease to disease progression and, if not progressed, to the previous control.

All the statistical analyses were performed using SPSS version 21.0, and $p<0.05$ was used to indicate

APPENDIX 1: Chemotherapy dose-administration Schedule.

GEMCIS	
Gemcitabine	1,000 mg/m^2 1 and 8th day
Cisplatin	100 mg/m^2 1st day
Every 21 days	
GEMOX	
Gemcitabine	1,000 mg/m^2 1 and 8th day
Oxaliplatin	85 mg/m^2 1st day
Every 21 days	
FOLFIRINOX	
5-FU infusion	2,400 mg/m^2 1 and 2nd day (46 hr infusion)
5-FU bolus	400 mg/m^2 1st day
Folinic asit	400 mg/m^2 1st day
Irinotecan	180 mg/m^2 1st day
Oxaliplatin	85 mg/m^2 1st day
Every 14 days	

5-FU: 5-Flouroprimidin; GEMCIS: Gemcitabine+Cisplatin; GEMOX: Gemcitabine+oxaliplatin; FOLFIRINOX: 5-flourouracil+oxaliplatin+irinotekan.

statistical significance. Bivariate correlation analysis and Kaplan-Meier survival analysis were used to evaluate the associations between chemotherapy regimens and survival. Chi-square tests were used to evaluate the associations between two verbal variables. Independent sample t-tests were used to evaluate the associations between the verbal and numerical variables.

RESULTS

The data of 67 patients diagnosed with unresectable metastatic PCa between January 2012 and January 2020 were evaluated retrospectively. The mean age (±standard deviation) in the whole group was 61.3±1.1 years, and 7.5% of the patients were >75 years old. At diagnosis, 77.6% of the patients had an ECOG score of 1, 22.4% had an ECOG score of 2, and none had an ECOG score of 0. A total of 68.7% of the patients were male. A total of 92.5% of the patients had de novo unresectable metastatic disease, and the others were diagnosed with recurrent metastasis. Four of the 5 patients with metastatic recurrence received medical adjuvant therapy after surgical treatment at the local stage. The average follow-up period was 11.8±2.2 months. The median OS was 8 months [inter quantile range (IQR); 3-13], and the median PFS was 6 months (IQR; 2-10) in the general group.

Patient and disease-related data were first evaluated via univariate analysis. Significant data in the univariate analysis were assessed by multivariate analysis (Table 1, Table 2). In the multivariate analysis, the sex distribution of the patients, the ECOG performance status at the time of diagnosis, and the presence of liver and lung metastases were evaluated for significant effects on OS.

There were 36 patients in the FOLFIRINOX group and 31 patients in the gemcitabine/platinum combination therapy group (18 patients in the GEMOX group and 13 patients in the GEMCIS group). The mean age was 57.6±8.5 years in the FOLFIRINOX group and 65.6±8.7 years in the gemcitabine plus platinum group (p<0.001). A comparison of the available patient and disease-related data between the two groups at the time of diagnosis is given in Table 3. The mean treatment dose (mg/m^2)

TABLE 1: Univariate Cox regression models to estimate overall survival.

Variable	HR	95% CI	p value
Age			
<65 years old	1.29	0.73-2.30	0.38
≥65 years old			
Gender			
Male	0.41	0.20-0.82	0.012*
Female			
Eastern Cooperative Oncology Group			
0-1	2.18	1.13-4.17	0.019*
≥2			
Stage at diagnosis			
Local-resectable	1.24	0.38-4.00	0.72
Locally advanced-unresectable/metastatic			
Adjuvant treatment			
Negative	0.69	0.17-2.86	0.61
Positive			
Biliary stent			
Yes	1.26	0.71-2.23	0.42
No			
Metastatic site			
Liver	1.93	1.00-3.11	0.049*
Lung	2.35	1.10-4.60	0.015*
Peritoneum	0.75	0.41-1.38	0.36
Bone	0.97	0.49-1.90	0.93
Chemotherapy			
FOLFIRINOX	0.70	0.4-1.22	0.20
Gemcitabine and platinum			

*Significant; HR: Hazard ratio; CI: Confidence interval.

TABLE 2: Multivariate Cox regression models to estimate overall survival.

Variable	HR	95% CI	p value
Gender			
Male	0.47	0.23-0.95	0.036*
Female			
Eastern Cooperative Oncology Group			
0-1	2.42	1.22-4.76	0.011*
≥2			
Metastatic site			
Liver	2.15	1.10-4.20	0.025*
Lung	2.27	1.13-4.58	0.021*
Peritoneum			
Bone			
Chemotherapy			
FOLFIRINOX	0.84	0.46-1.55	0.58
Gemcitabine and platinum			

*Significant; HR: Hazard ratio; CI: Confidence interval.

TABLE 3: Patient-related data.

	FOLFIRINOX	Gemcitabine and platin	
Age (X±SD)	57.6±8.5	65.6±8.7	p<0.001*
Gender % (n)	Male 58.3% (21)	Male 80.6% (25)	p=0.05
	Female 41.7% (15)	Female 19.4% (6)	
Eastern Cooperative Oncology Group % (n)	1-77.8% (28)	1-77.4% (24)	p=0.97
	2-22.2% (8)	2-22.6% (7)	
Stage % (n)	Resectable 11.1% (4)	Resectable 3.2% (1)	p=0.4
	Unresectable-metastatic 88.9% (32)	Unresectable-metastatic 96.8% (30)	
Adjuvant treatment % (n)	Negative 88.9% (32)	Negative 100% (31)	p=0.056
	Positive 11.1% (4)		

*Significant; SD: Standard deviation.

and the median number of cycles received for each drug in the two groups of patients are shown in Table 4.

Moreover, there was no statistically significant difference in the median OS between the two groups (OS: 11 months vs. 7 months; p=0.192) (Figure 1). Similarly, no significant difference was found in the median PFS duration (PFS: 6 months vs. 6 months; p=0.22) (Figure 2). In the FOLFIRINOX group, the OS at 12 months was greater than that in the group receiving gemcitabine and platinum (12-month OS; 30% vs. 25%). Similarly, there was a difference in 12-month PFS between the FOLFIRINOX and gemcitabine platinum groups (12-month PFS; 19.4% vs. 9.6%). When the best responses after the two treatment groups were evaluated, 50% of the patients in the FOLFIRINOX group achieved a PR, and 11.1% had SD. In the gemcitabine platinum group, 38.7% of the patients achieved a PR, and 22.6% had SD. The DCR (78.6% vs. 73.1%, respectively; p=0.64) and ORR (64.3% vs. 46.2%, respectively; p=0.180) were

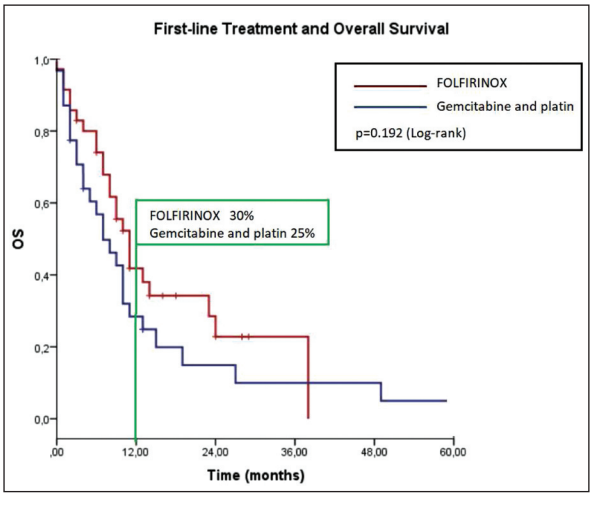

FIGURE 1: OS and first-line treatment.
OS: Overall survival.

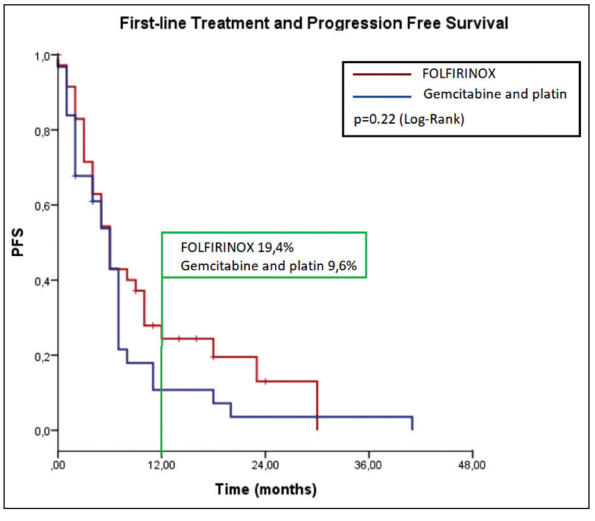

FIGURE 2: PFS and first-line treatment.
PFS: Progression free survival.

TABLE 4: First-line treatment exposure.

Chemotherapy	Dose	Number of cycles
FOLFIRINOX		
5-FU bolus (minimum-maximum)	382 mg/m^2 (300-400)	5 (1-12)
5-FU infusion (minimum-maximum)	2,400 mg/m^2 (1,625-2,400)	4.5 (1-12)
Irinotecan (minimum-maximum)	165 mg/m^2 (90-180)	5 (1-12)
Oxaliplatin (minimum-maximum)	80 mg/m^2 (60-85)	5 (1-12)
GEMCIS		
Gemcitabine (minimum-maximum)	1,000 mg/m^2 (750-1,200)	4 (1-6)
Cisplatin (minimum-maximum)	76 mg/m^2 (55-100)	4 (1-6)
GEMOX		
Gemcitabine (minimum-maximum)	1,000 mg/m^2 (740-1,200)	5 (1-9)
Oxaliplatin (minimum-maximum)	70 mg/m^2 (50-75)	4 (1-6)

not significantly different between the two groups.

In the whole cohort, 86.6% (58) of the patients had PD after first-line treatment, and 48.3% (28) of these patients could receive second-line therapy. Approximately 93% (29) of the patients in the gemcitabine and platinum groups had PD, and 44.8% (13) received second-line therapy. Similarly, 80.6% (29) of the patients in the FOLFIRINOX group had PD, and 51.7% (15) received 2nd-line therapy. There was no statistically significant difference between these results (p=0.6). Primary GCSF prophylaxis was used in 94.4% of the patients in the FOLFIRINOX group, while primary prophylaxis was used in 23.3% of the patients in the gemcitabine/platinum treatment group (p<0.001). Common side effects (Grades 1-4) and their statistical comparisons between the two groups are given in Table 5. The incidence of neutropenia fever, mucositis, diarrhea, and neuropathy was significantly greater in the FOLFIRINOX group (p=0.036, p=0.021, p=0.009, and p=0.021, respectively). There was no significant difference between the two groups in terms of Grade 3-4 side effects, interruption of treatment due to side effects or discontinuation of treatment (p=0.60, p=0.33, p=0.8, respectively). There were no detectable treatment-related deaths in either group.

DISCUSSION

Our single-institution retrospective study compared the efficacy of FOLFIRINOX and gemcitabine in combination for unresectable metastatic PCa. PCa patients are often diagnosed on the basis of a poor performance score and short life expectancy, and palliation is the primary goal of treatment in advanced stages. Even though the treatment schemes that started with 5-FU and gemcitabine in the 1980s left their place to use two-agent, three-agent intensive cytotoxic treatments, the OS duration is still approximately 12 months.

In 2011, compared with gemcitabine, FOLFIRINOX significantly improved OS (11.1 vs. 6.8 mo), PFS (6.4 vs. 3.3 mo), and the response rate (31.6 vs. 9.4%).[8] Currently, no single treatment modality can prolong survival in patients receiving first-line treatment for unresectable metastatic PCa. The recruitment criteria for this Phase III study included an ECOG performance score of 0-1 and age <75 years.[8] However, in real life, some patients are more fragile in clinical practice. One of the differences in our study is that 7.5% of the patients were 75 years old and older, 22.4% had an ECOG score of 2, and no patient had an ECOG score of 0. Variations in sex, ECOG performance status, and rates of liver and lung metastases between the two treatment cohorts might have influenced physicians' choices of chemotherapy, thereby affecting survival outcomes. However, given that this investigation incorporates data from real-life scenarios, addressing these disparities aligns with the objective of our study. Moreover, the OS figures in the FOLFIRINOX cohort were comparable to those reported in the French trial. In the current study, although a numerical advantage of four months for FOLFIRINOX was observed, no statistically significant difference in OS was detected between patients administered FOLFIRINOX and those receiving gemcitabine plus platinum. The number of patients was considered one of the reasons for this difference. Second, the proportion of patients receiving second-line therapy might have affected the results.

Unlike in the French trial, in our patient group, gemcitabine was used in combination with platinum rather than as a single agent. The PFS of patients in the gemcitabine single-agent group in the French trial was 3.3 months. However, PFS reached 6 months with the addition of platinum to gemcitabine in our study. Therefore, there was no significant difference in PFS between patients treated with FOLFIRINOX

TABLE 5: Treatment-related adverse events.

FOLFIRINOX % (n)		GEMOX % (n)	
Anemia	8.3 (3)	6.4 (2)	0.2
Neutropenia	61.1 (22)	38.7 (12)	0.067
Neutropenic fever	30.6 (11)	9.7 (3)	*0.036
Thrombocytopenia	72.2 (26)	63.3 (19)	0.44
Mucositis	61.1 (22)	38.7 (12)	*0.021
Diarrhea	19.4 (7)	0 (0)	*0.009
Neuropathy	33.3 (12)	9.7 (3)	*0.021
Kidney dysfunction	8.6 (3)	16.1 (5)	0.35
Grade 3-4 adverse event	41.7 (15)	35.5 (11)	0.60
Interrupting treatment	44.1 (15)	32.3 (10)	0.33
Discontinuation	29.4 (10)	32.3 (10)	0.8

*Significant.

and patients treated with gemcitabine. In the Phase II study, the DCR was determined to be 65% in the FOLFIRINOX group, and this rate was similar to that in our study.[7] Furthermore, in our study, a similar DCR was achieved with the combination of gemcitabine and platinum, and no significant difference was detected compared with that in the FOLFIRINOX group.

Gemcitabine plus nab-paclitaxel was also started as a first-line treatment after 2013 in the IMPACT study.[11] Although the patient groups were different, the survival of patients treated with gemcitabine plus nab-paclitaxel in the Phase III study was lower than that of patients treated with FOLFIRINOX in the French trial. Retrospective studies comparing FOLFIRINOX and gemcitabine plus nab-paclitaxel have been performed. One of them was published in 2017, and gemcitabine plus nab-paclitaxel, FOLFIRINOX, and gemcitabine were compared in this study.[12] While PFS and OS were similar for patients treated with gemcitabine plus nab-paclitaxel and FOLFIRINOX, both regimens were significantly superior to single-agent therapy. However, in this study, there were no arms treated with gemcitabine or platinum agents in combination.

In a single-center study published in 2021, the treatment regimens gemcitabine plus nab-paclitaxel, FOLFIRINOX, and GEMOX were compared retrospectively. The median OS and PFS were similar among the 3 groups in the present study (OS: 11.1 vs. 10.1 vs. 10.2 months; PFS: 4.9 vs. 3.7 vs. 4.7 months.[13] In our study, the OS and PFS of patients in the FOLFIRINOX and gemcitabine platinum groups were similar, and these results support our study.

In many retrospective studies in the literature, the amount of patients who can take the current regimens according to the doses defined in the phase studies has not been stated.[12-15] Fragile patient groups treated in clinical practice cannot be treated at the planned dose. In our study, patients in both treatment groups could use treatment agents at a dose average lower than the dose per cycle specified in Phase II-III trials. Likewise, both treatment groups received fewer cycles than the number of cycles recommended. This situation should be considered when evaluating patients in real life.

The primary reason for patients not receiving treatment at the planned intensity is side effects. A study comparing the GEMOX regimen and FOLFIRINOX regimen revealed neutropenia and neuropathy more frequently in the FOLFIRINOX group, while thrombocytopenia was more common in the GEMOX combination group.[13] In our study, mucositis, neutropenia, and neuropathy were observed in the gemcitabine plus platinum group at a similar rate to that in the literature.[16] These side effects were also detected more frequently in patients receiving FOLFIRINOX compared to those receiving gemcitabine platinum, which is consistent with the literature.[16] However, thrombocytopenia has been detected more frequently than in the literature, and diarrhea is less common than in the literature.[4-6] In our study, the combination of gemcitabine and platinum-enhanced chemotherapy seemed more tolerable than FOLFIRINOX group.

When the side effect profile of the Phase II FOLFIRINOX trial was evaluated, Grade 3-4 neutropenia was detected in 52% of the patients, but neutropenic fever was seen in only 4%. Further, 8% of the patients needed hospitalization for diarrhea, and 28% had neuropathy of any grade. Treatment was terminated in 7 out of the 46 patients due to neuropathy.[7] In our study, the incidences of Grade 3-4 side effects and the rates of interruption and discontinuation of treatment due to side effects were similar in both groups. Although GCSF was used at a high rate as primary prophylaxis in the FOLFIRINOX group, neutropenic fever was observed at a rate of 30.6%. Furthermore, this ratio is higher than that for both gemcitabine/platinum combinations and rates defined in the literature. This increase was thought to be caused by the inclusion of patients >75 years of age and patients with poor performance scores.

Among the limitations of our study are its retrospective nature, the relatively low number of patients and the potential for selection bias due to chemotherapy choices being based on physician preferences. However, to the best of our knowledge, there are no retrospective studies involving larger numbers of patients in the literature. Another limitation is the lack

of knowledge in our study about second-line chemotherapy regimens that could impact OS. Future studies could include additional patients.

CONCLUSION

As a result, although there was a 4 month OS advantage in favor of FOLFIRINOX, no statistically significant difference was found in the median OS, PFS, and DCR. Considering the side effect profiles, neutropenic fever, diarrhea, mucositis, and neuropathy were found more frequently in the FOLFIRINOX group despite primary GCSF prophylaxis. Our study was not designed to examine this directly; however, gemcitabine platinum combination can be used instead of single-agent gemcitabine for patients who cannot be treated with FOLFIRINOX first-line without worsening the side effect profile and providing similar PFS. It needs to be supported by prospective studies with higher patient numbers.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bediz Kurt İnci;* ***Design:*** *Bediz Kurt İnci;* ***Control/Supervision:*** *Ozan Yazıcı, Nuriye Özdemir;* ***Data Collection and/or Processing:*** *Fatih Gürler;* ***Analysis and/or Interpretation:*** *Osman Sütcüoğlu;* ***Literature Review:*** *Volkan Aslan;* ***Writing the Article:*** *Bediz Kurt İnci;* ***Critical Review:*** *Ahmet Özet, Aytuğ Üner;* ***References and Fundings:*** *Oktay Ünsal.*

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7-30. [Crossref] [PubMed]
2. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020;395(10242):2008-2020. [Crossref] [PubMed]
3. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403-2413. Corrected and republished in: J Clin Oncol. 2023;41(36):5482-5492. [Crossref] [PubMed]
4. Louvet C, Labianca R, Hammel P, et al; GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol. 2005;23(15):3509-3516. [Crossref] [PubMed]
5. Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs. 1994;12(1):29-34. [Crossref] [PubMed]
6. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol. 2006;24(24):3946-3952. [Crossref] [PubMed]
7. Conroy T, Paillot B, François E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol. 2005;23(6):1228-1236. [Crossref] [PubMed]
8. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-1825. [Crossref] [PubMed]
9. Ducreux M, Cuhna AS, Caramella C, et al; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v56-68. Erratum in: Ann Oncol. 2017;28(suppl_4):iv167-iv168. [Crossref] [PubMed]
10. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. Eur J Cancer. 2013;49(3):593-603. [Crossref] [PubMed]
11. Von Hoff DD, Ervin TJ, Arena FP, et al. Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates. American Society of Clinical Oncology. 2013;31:4005. [Crossref]
12. Wang Y, Camateros P, Cheung WY. A Real-World Comparison of FOLFIRINOX, Gemcitabine Plus nab-Paclitaxel, and gemcitabine in advanced pancreatic cancers. J Gastrointest Cancer. 2019;50(1):62-68. [Crossref] [PubMed]
13. Quan Q, Wang Y, Wang F, et al. Real world first-line treatments and outcomes of nab-paclitaxel plus gemcitabine, mFOLFIRINOX and GEMOX in unresectable pancreatic cancer from a Chinese Single Institution. Curr Oncol. 2020;28(1):209-219. [Crossref] [PubMed] [PMC]
14. Chan KKW, Guo H, Cheng S, et al. Real-world outcomes of FOLFIRINOX vs gemcitabine and nab-paclitaxel in advanced pancreatic cancer: a population-based propensity score-weighted analysis. Cancer Med. 2020;9(1):160-169. [Crossref] [PubMed] [PMC]
15. Kayahan N, Karaca M, Satış H, Yapar D, Özet A. Folfirinox versus gemcitabine-cisplatin combination as first-line therapy in treatment of pancreaticobiliary cancer. Turk J Med Sci. 2021;51(4):1727-1732. [Crossref] [PubMed] [PMC]
16. Caglevic C, Mahave M, Sanhueza C, Ubillos L. Current systemic treatment options for metastatic and unresectable pancreatic cancer. Pancreatic Cancer. IntechOpen; 2020. [Crossref]