Original Article

Comparison of Adjuvant Modified FOLFIRINOX with Other Adjuvant Chemotherapies in Resected Pancreatic Adenocarcinoma: Real-Life Data

Rezeke Edilmiş Pankreas Adenokarsinomda Adjuvan Modifiye FOLFİRİNOX'un Diğer Adjuvan Kemoterapilerle Karşılaştırılması: Gerçek Yaşam Verisi

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ABSTRACT

Background: Pancreatic cancer is among the cancers with the worst prognosis and therefore adjuvant treatment is very important for reducing mortality. The aim of this study is to compare the gold standard mFolfirinox regimen with other treatment regimens in the adjuvant treatment of pancreatic cancer in real-world practice.

Materials and methods: Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study as two groups, mFolfirinox and Others (at a ratio of 1:2). The primary endpoint was disease-free survival (DFS). Secondary endpoints were determined as overall survival (OS), predictive factors, and safety.

Results: Data of 166 patients were collected from five oncology centers. With a median follow-up of 30.3 months (24.6-35.9), the estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p=0.464). Better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox.

Conclusion: In the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit.

Keywords: Pancreatic adenocarcinoma, modified folfirinox, adjuvant chemotherapy, real-life experience

ÖZET

Amaç: Pankreas kanseri prognozu en kötü olan kanserler arasında yer alır ve bu nedenle adjuvan tedavi mortaliteyi azaltmak için çok önemlidir. Bu çalışmanın amacı, gerçek dünya pratiğinde pankreas kanserinin adjuvan tedavisinde altın standart mFolfirinox rejimini diğer tedavi rejimleriyle karşılaştırmaktır.

Gereç ve yöntem: Pankreas kanseri rezeksiyonu yapılan ve en az bir doz adjuvan kemoterapi alan hastalar mFolfirinox ve Diğerleri (1:2 oranında) olmak üzere iki grup olarak çalışmaya alındı. Birincil sonlanım noktası hastalıksız sağkalımdı (DFS). İkincil sonlanım noktaları, genel sağkalım (OS), prediktif faktörler ve güvenlik olarak belirlendi.

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Bulgular: Beş onkoloji merkezinden 166 hastanın verileri toplandı. Ortanca 30,3 aylık (24,6-35,9) takipte, tahmini ortanca DFS, mFolfirinox grubunda 17,9 ay (%95 GA, 10,3-25,6) ve diğerleri grubunda 12,5 ay (%95 GA, 9,7-15,3) olarak saptandı (p = 0.088). Tahmini ortanca OS, mFolfirinox grubunda 30,7 ay (%95 GA, 15,7-45,7), diğerleri grubunda 22 aydı (%95 GA, 16-27,9) (p=0,464). Daha iyi ECOG performans durumu, tümörün baş ve ampulla dışında yerleşimi, evre 1 ve 2B, adjuvan kemoradyoterapi (CRT) almama ve perinöral invazyon, mFolfirinox lehine hastalıksız sağkalım avantajı sağladı.
Sonuç: Rezeke edilmiş pankreas kanserinin adjuvan tedavisinde, mFolfirinox rejimi istatistiksel olarak önemsiz, ancak klinik olarak anlamlı bir DFS ve OS faydası sağladı.

Anahtar Kelimeler: Pankreas adenokarsinomu, modifiye folfirinox, adjuvan kemoterapi, gerçek yaşam deneyimi

Introduction

Pancreatic cancer is among the cancers with the worst prognosis and has an important place among cancer-related deaths [1, 2]. Minimal survival improvement has been achieved in the last few decades [3]. Although surgery is the only option for cure, 5-year survival rates are around 10% with surgery alone [4]. This low survival rate with surgery alone has led to the development of adjuvant treatment strategies. Gemcitabine was used in adjuvant therapy, which is an important drug in the treatment of metastatic pancreatic cancer, and in the landmark study phase-III CONKO-1, there was a significant improvement in median disease-free survival (DFS) with gemcitabine compared to surgery alone (13.4 months vs. 6.7 months p<0.001) [4]. With this study, gemcitabine remained the standard adjuvant therapy for a long time. The ESPAC-4 trial compared gemcitabine with the combination of gemcitabine and capecitabine in adjuvant therapy following the CONKO-1 trial. Median survival was 28 months to 25.5 months, with moderate significance in favor of combination therapy (p = 0.032) [5]. In the APACT trial which was recently presented, the adjuvant gemcitabine plus nab-paclitaxel study did not meet the primary endpoint of independently assessed DFS gemcitabine [6]. The combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (Folfirinox regimen) resulted in longer overall survival than gemcitabine when administered as first-line treatment in patients with metastatic pancreatic cancer [7]. Based on these results, the PRODIGE-24 phase III study was planned to investigate the efficacy of gemcitabine versus Folfirinox regimen in adjuvant treatment after pancreatic cancer resection [8]. In this study, the median disease-free survival was 21.6 months versus 12.8 months in favor of Folfirinox regimen, and the median survival was 54.4 months versus 35 months, respectively. Despite its apparent clinical efficacy, the Folfirinox chemotherapy regimen had high treatment toxicity. In this study, the efficacy was achieved by considering more toxicity. Because of this toxicity, the dose of irinotecan was reduced by removing the bolus 5-Fluorouracil, and this modified form (mFolfirinox) has become the gold standard for adjuvant therapy in patients with good performance in pancreatic adenocarcinoma. However, in real-life, patients are not treated with strict rules as in clinical trials [9]. There are many patient groups that were not included in the clinical trial. Therefore, real-life data are important to shed light on the treatment of these patient groups and also to confirm the results of clinical trials. We planned this retrospective real-life study to compare the gold standard mFolfirinox regimen with other treatment regimens in adjuvant treatment of pancreatic cancer.

Materials and Methods

Patients and design

This is a multi-center retrospective study. Study data were obtained retrospectively from patient files and hospital records. Ethical approval was obtained from the ethics committee of Ankara City Hospital, with the date of 08.06.2022 and number E2-22-1969, before starting study. The study was conducted in accordance with ethical rules,

the Declaration of Helsinki and good clinical practice guidelines.

In our study, patient data were obtained from five high-volume tertiary oncology centers. Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study. All patients aged 18 years and older were included in the study. Patients who underwent R2 resection were allowed. Patients who received chemoradiotherapy in adjuvant treatment were also included in the study. The study was based on the comparison of two groups of patients, mFolfirinox and Others. In the study, which included patients at a ratio of 1:2, respectively, clinical, pathological and treatment information of the patients were collected. Data that are thought to be predictive factors were examined. The neutrophil to lymphocyte ratio (NLR), one of these factors, was calculated by dividing the neutrophil count by the lymphocyte count in complete blood count. The primary endpoint was disease-free survival. Secondary endpoints were determined as overall survival (OS), predictive factors, and safety. DFS was defined as the time from initiation of adjuvant treatment to recurrence/metastasis or death. OS was defined as the time from initiation of adjuvant treatment to death. The data of the patients who were not followed up were not used in the DFS analysis. The survival results of these patients were confirmed by checking the system of the Ministry of Health. Adverse events have been evaluated according to The Common Terminology Criteria for Adverse Events (CTCAE).

Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics Version 25 program (SPSS Inc., Chicago, IL, USA). A median value and minimum-maximum values were used to determine continuous variables. Categorical variables were shown as numbers and percentages. The difference between the ages of the patients was evaluated with independent t-test, the difference of histologies and surgical margins between groups with the Fisher's exact test, and the differences of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) values between groups were evaluated with the Mann-Whitney U test. Differences between groups other than these were evaluated with the chi-square test. Survival was univariately analyzed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups.

Results

Data of 166 patients were collected from 5 oncology centers at a ratio of 1:2 (mFolfirinox vs. others). The vast majority of patients in the others group received gemcitabine-based therapies as adjuvant treatment. 35.7% of patients (n= 40) were treated with gemcitabine plus capecitabine, 57.1% of patients (n = 64) were treated with single-agent gemcitabine, and 7.2% of patients (n = 8) were treated with other chemotherapy regimens. The median age at diagnosis of the patients was 57 (18-71) years and 63 (34-75) years for the mFolfirinox group and others group, respectively. The ≥ 65-year-old rate was 13% in the mFolfirinox group and 45% in the others group. There was no difference between the baseline characteristics of the patients, except for age, ECOG (Eastern cooperative oncology group) performance scores, whether or not they received adjuvant chemoradiotherapy, and postoperative CEA/CA19-9 values (Table 1).

Treatment and efficacy

The median duration of treatment was median 23.6 weeks (2 to 39.3) in the mFolfirinox group and 18.9 weeks (1 to 43.4) in the others group (p = 0.06). With a median follow-up of 30.3 months (24.6-35.9), 70% (n = 98) of all patients had an event for DFS, and 57.2% (n = 95) of patients died. The estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088) (Figure 1). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p = 0.464) (Figure 1). DFS rates at 12 months were

Table 1. Patient characteristics

	mFolfirinox group n= 54		Others group N=112		p value
Median age – years, *(range)*	57 (18 – 71)		63 (34 – 75)		< 0.001
≥ 65 years – n, (%)	7	*(13)*	49	*(45)*	< 0.001
Histology – n, (%)					0.55
Adenocarcinoma	54	*(100)*	109	*(97)*	
Other			3	*(3)*	
Stage – n, (%)					0.10
1	8	*(15)*	19	*(17)*	
2A	4	*(7)*	18	*(16)*	
2B	23	*(43)*	56	*(50)*	
3	17	*(32)*	19	*(17)*	
Missing	2	*(4)*			
Surgical margins – n, (%)					0.25
R0	41	*(76)*	88	*(79)*	
R1	10	*(19)*	18	*(16)*	
R2	0	*(0)*	6	*(5)*	
Missing	3	*(6)*			
Tumor location – n, (%)					0.15
Head	33	*(61)*	73	*(65)*	
Ampulla	14	*(26)*	16	*(14)*	
Other	7	*(13)*	22	*(21)*	
Lymphovascular invasion – n, (%)	36	*(67)*	72	*(64)*	0.81
Perineural invasion – n, (%)	46	*(85)*	93	*(83)*	0.61
ECOG performance status – n, (%)					0.002
0 - 1	48	*(89)*	87	*(78)*	
2	4	*(7)*	25	*(22)*	
Missing	2	*(4)*			
Adjuvant CRT – n, (%)					0.001
No	38	*(70)*	49	*(44)*	
Yes	16	*(30)*	63	*(56)*	
Median CEA – ng/mL,*(range)*	1.6 *(0.5-35.6)*		2.5 *(0.2-1123)*		0.002
Median CA19-9 – U/mL, (*range)*	32 *(1-3303)*		65 *(0.6-42010)*		0.004

mFolfirinox = Modified folfirinox, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, CEA = Carcinoembryonic antigen, CA19-9 = Carbohydrate antigen 19-9.

51.9% (n=27) and 53.4% (n=47) in the mFolfirinox group and in the others group (p = 0.502), respectively.

Predictive factors

In subgroup analysis, better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox. In addition, in moderately differentiated histology and the NLR value being higher than the median value, a significant p value was found at the border. No difference was found between the groups in other subgroups (Table 2). In the overall survival analysis of the subgroups, no difference was found between mFolfirinox and other treatments in any group (Table 3).

Safety

Dose delay and dose reduction requirements were 67.9% (n=36) and 58.5% (n=31) in the mFolfirinox group, compared with 15.4% (n=16) and 12.6% (n = 13) in the others group, respectively (dose delay p<0.001, dose reduction p<0.001). Adverse events of any degree were seen in 92.3% in the mFolfirinox group, while 39.4% in the others group (p<0.001). Grade 3 or 4 adverse events were reported 51.9% in the mFolfirinox group, compared with 10.6% in the others group (p<0.001). The most common grade 3-4 adverse events in the mFolfirinox group were neutropenia (38.5%) and anemia (15.4%),

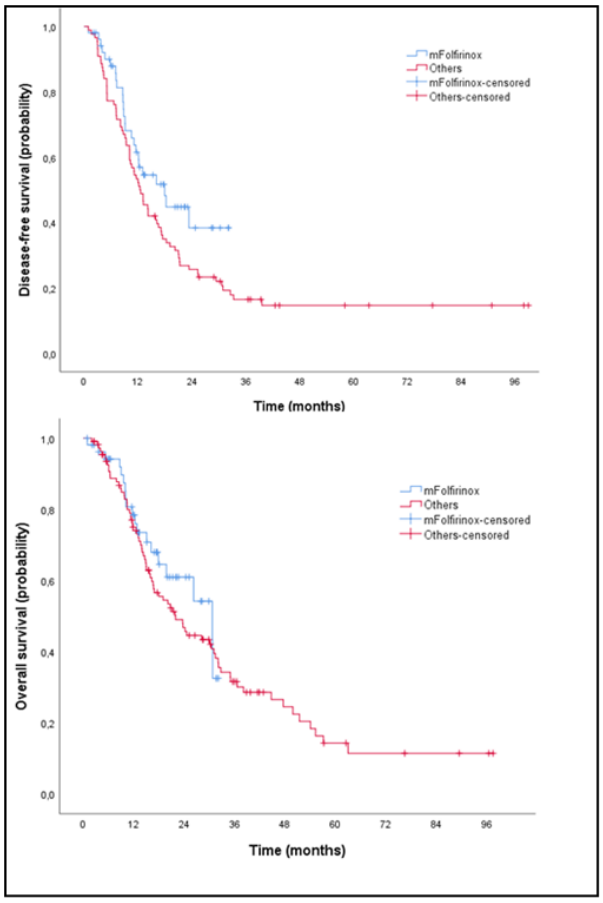

Figure 1. Kaplan-meier curves for disease-free survival and overall survival

compared with neutropenia (8.7%), anemia (3.8%) in the others group. One patient died in the mFolfirinox group due to treatment toxicity.

Discussion

The prognosis of pancreatic cancer is poor due to late diagnosis and aggressive nature [2, 10, 11]. Surgery remains the only curative treatment in resectable tumors. In addition to surgery, the cure rate is increased with adjuvant treatment [3, 12, 13]. Many clinical studies have investigated the results of various adjuvant treatment regimens [14]. However, the optimal multidisciplinary treatment strategy was controversial until the PRODIGE-24 phase 3 study, published in December 2018 [8]. Although there are still controversial points, with this study the mFolfirinox regimen became the gold standard in the adjuvant treatment of pancreatic cancer. In the adjuvant treatment of resected pancreatic cancer in our study, we found a clinically significant difference with the mFolfirinox regimen in median DFS of 17.9 months vs. 12.5 months compared to the other treatments, although it was not statistically significant. We also found a clinically significant, statistically insignificant difference in favor of mFolfirinox in overall survival of approximately 9 months. The mFolfirinox and other groups were generally well balanced, however, the mFolfirinox group consisted of younger, better ECOG performance scores, less treated with chemoradiotherapy, and had lower median CEA/CA 19-9 levels. The fact that fit patients, not exposed to chemoradiotherapy toxicity and had lower postoperative tumor markers were in the mFolfirinox group may have created a potential selection bias. However, the median DFS and OS of the others group were similar to both previous phase 3 studies [4, 5, 8, 15, 16] and real-life data [17, 18]. In the 5-year results of the recently published pivotal phase III trial, the median DFS was reported as 21.4 months and the median overall survival was 53.5 months [19]. In our study, DFS and especially OS in the mFolfirinox group were found to be lower than in the phase III pivotal clinical trial. Real-life data on the use of the mFolfirinox regimen in adjuvant treatment are very limited. In a small number of real-life studies, we see that very few patients use the mFolfirinox regimen for adjuvant treatment [20]. In our study, it is not surprising that the outcomes of patients in clinical practice were worse than in clinical trial. In the PRODIGE-24 study, all patients had an ECOG performance score of 0-1, while in our mFolfirinox group, 7% of patients had an ECOG performance score of 2. In addition, patients with stage III or CA 19-9 levels above 180 were excluded from the PRODIGE-24 study. In our study, 32% of the patients were stage III, and there were patients with high CA 19-9 levels. And we know that poor performance score, advanced stage and high CA 19-9 levels are associated with poor prognosis [17]. For this reasons, we can say that the differences in outcomes between mFolfirinox and the others group are not only

Table 2. Effects of treatments on disease-free survival in subgroup analysis

	mFolfirinox group Median DFS (95% CI), months	Others group Median DFS (95% CI), months	p value
Age			
< 65 years	18.3 (6.7 to 29.8)	13.2 (11.2 to 15.1)	0.127
≥ 65 years	17.6 (13.2 to 22)	11.2 (6.5 to 15.7)	0.208
ECOG performance status			
0 - 1	23.3 (1 to 32.2)	13.2 (10.9 to 15.4)	0.023
2	8.6 (0.6 to 16.5)	11.6 (7.3 to 15.9)	0.908
Tumor grade			
Well differentiated	*	17.5 (4.6 to 30.3)	0.18
Moderately differentiated	18.3 (12 to 24.5)	12.4 (9.1 to 15.9)	0.055
Poorly differentiated	11.1 (8.1 to 14.2)	10.1 (6.7 to 13.4)	0.856
Tumor location			
Head	12.2 (5.1 to 19.1)	12.4 (8.9 to 15.9)	0.728
Ampulla	*	23.3 (7.5 to 39.2)	0.226
Other	*	10.3 (8.2 to 12.5)	0.045
Stage			
1	*	*	0.036
2A	*	14.2 (10.6 to 17.9)	0.512
2B	*	11.2 (8.6 to 13.8)	0.007
3	10.6 (7.7 to 13.5)	8.7 (3.5 to 13.9)	0.741
Surgical margins			
R0	23.3 (14.7 to 31.9)	14.2 (10.3 to 18.1)	0.082
R1	*	7.1 (2.8 to 11.4)	0.111
R2	N/A	8.1 (0.04 to 16.1)	N/A
Adjuvant CRT			
No	23.3 (*)	13.2 (9.1 to 17.3)	0.03
Yes	17.9 (8.9 to 26.9)	11.1 (7.8 to 14.5)	0.481
Body mass index			
< 18.5	11.5 (0.1 to 27.4)	12.2 (6.9 to 17.4)	0.364
18.5 - 24.9	16.1 (7.9 to 24.2)	13.1 (5.5 to 20.9)	0.545
≥ 25	*	12.6 (8.3 to 16.9)	0.104
Smoking history			
No	13.1 (6.6 to 19.4)	12 (5.9 to 18)	0.442
Yes	23.3 (7 to 39.6)	12.5 (10.3 to 14.6)	0.107
NLR			
≤ median	13.1 (5.4 to 20.7)	12 (7.9 to 16.1)	0.511
> median	23.3 (11.1 to 35.5)	13.2 (10.1 to 16.3)	0.06
Postoperative CA19-9 level			
≤ ULN**	*	17.1 (5.8 to 28.5)	0.129
> ULN	12.1 (6.6 to 17.8)	12.1 (9.8 to 14.5)	0.213
Lymphovascular invasion			
No	*	17.5 (5.6 to 29.4)	0.09
Yes	17.9 (6.5 to 29.3)	12 (9.7 to 14.3)	0.156
Perineural invasion			
No	*	39.6 (23.1 to 56.1)	0.466
Yes	17.9 (9 to 26.8)	11.6 (9.7 to 13.5)	0.016

*mFolfirinox = Modified folfirinox, DFS = Disease-free survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

Table 3. Effects of treatments on overall survival in subgroup analysis

	mFolfirinox group Median OS (95% CI), months	Others group Median OS (95% CI), months	p value
Age			
< 65 years	30.7 (15.5 to 45.9)	20.7 (13 to 28.5)	0.28
≥ 65 years	*	23.7 (10.8 to 36.6)	0.627
ECOG performance status			
0 - 1	30.7 (16.6 to 44.7)	24.2 (14.3 to 34.1)	0.6
2	10.1 (*)	16.3 (10.8 to 21.6)	0.916
Tumor grade			
Well differentiated	*	44.7 (12.1 to 77.4)	0.494
Moderately differentiated	30.7 (11.9 to 49.5)	21.2 (15.9 to 26.5)	0.235
Poorly differentiated	12.3 (8.7 to 15.9)	14 (8.4 to 19.6)	0.284
Tumor location			
Head	26.3 (11 to 41.5)	20.7 (15.4 to 26.1)	0.506
Ampulla	*	36.6 (14.2 to 59)	0.249
Other	*	23.7 (12.4 to 34.9)	0.216
Stage			
1	*	32.1 (0.6 to 63.6)	0.252
2A	*	*	0.424
2B	30.7 (24.2 to 37.2)	21.2 (13.9 to 28.5)	0.288
3	15.1 (5.8 to 24.3)	12.8 (9.9 to 15.8)	0.936
Surgical margins			
R0	30.8 (18.2 to 43.4)	24.6 (15.1 to 34.1)	0.508
R1	*	23.7 (9.6 to 37.4)	0.847
R2	N/A	9.1 (2.7 to 15.3)	N/A
Adjuvant CRT			
No	30.7 (22.7 to 38.6)	31.1 (26.1 to 36.1)	0.57
Yes	30.1 (17.1 to 44.5)	16.6 (11.7 to 21.6)	0.317
Body mass index			
< 18.5	15.1 (*)	11.7 (*)	0.535
18.5 - 24.9	30.7 (14.4 to 47)	22 (13.3 to 30.6)	0.754
≥ 25	*	31.1 (12.5 to 49.6)	0.394
Smoking history			
No	*	20.1 (11.4 to 28.8)	0.335
Yes	30.7 (19.2 to 42.2)	30.1 (16.8 to 43.4)	0.918
NLR			
≤ median	30.8 (14.7 to 46.8)	23.7 (8.6 to 38.8)	0.929
> median	30.7 (15.1 to 46.2)	16.7 (10.7 to 22.7)	0.154
Postoperative CA19-9 level			
≤ ULN**	30.7 (*)	30.5 (16.3 to 44.7)	0.592
> ULN	26.3 (8.7 to 43.8)	16.7 (10.8 to 22.6)	0.622
Lymphovascular invasion			
No	*	30.1 (21.1 to 39.1)	0.517
Yes	30.7 (10.1 to 51.3)	19 (12.6 to 25.4)	0.626
Perineural invasion			
No	*	63 (35 to 91)	0.937
Yes	30.7 (16.3 to 45.1)	19 (12.4 to 25.6)	0.331

*mFolfirinox = Modified folfirinox, OS = Overall survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

due to selection bias, but are the effectiveness of mFolfirinox.

In subgroup analysis, it is predicted DFS advantage with mFolfirinox in the patients with ECOG performance status 0-1, tumors located in the pancreatic body and tail, stage I and IIB tumors, the patients who do not receive adjuvant chemoradiotherapy and tumors with perineural invasion. The efficacy of mFolfirinox in patients with an ECOG performance score of 2 compared to other regimens is not clear, as all patients in the PRODIGE-24 study were patients with an ECOG performance score of 0-1 [8]. Despite the small number of patients, we did not find any difference between treatment regimens in patients with an ECOG performance score of 2 in our study. These results suggest that this regimen should be considered in fit patients.

Chemotherapy is generally avoided in elderly patients [21]. However, elderly patients have been shown to benefit similarly from chemotherapy [22]. While patients ≥ 65 years of age benefited from mFolfirinox treatment in the pivotal trial, we found no difference between treatment regimens in patients ≥ 65 years of age in our real-life study. Based on these results, it may be a good option to consider less toxic regimens for elderly patients.

The use of adjuvant CRT, in the era of mFolfirinox, is controversial. It can generally be used in patients with positive surgical margins or lymph nodes. In our study, the outcomes of patients who did not receive adjuvant CRT were numerically higher than the patients who received it. This is the result of increasing treatment toxicity and adversely affecting survival. Also, there is no difference between the treatment regimens.

While we expect mFolfirinox, which is considered to be a more effective treatment, to have better survival in patients with poor prognostic factors (poorly differentiated, stage III, R1 resection, high NLR, postoperative high CA19-9 level, and lymphovascular invasion), unlike the pivotal study, no difference was found with other treatment regimens in our study. This may be due to the different patient population and treatment regimens.

As expected, the safety profile of the mFolfirinox regimen was less favorable than other adjuvant treatments. We found that we obtained this non-significant difference in survival outcomes in favor of mFolfirinox with higher treatment-related adverse events. In the PRODIGE-24 study, grade 3-4 adverse events were seen in 75.9% of patients, this rate was 51.9% in our study. Adverse events were lower than in the clinical trial, but slightly higher than in real-life data. In a retrospective study reported from China, dose reduction with mFolfirinox was found to be 41.2%, while in our study it was found to be 67.9% [23]. Toxicity is not only an important problem in the acute period. It may shorten the duration of treatment, leading to early discontinuation of adjuvant therapy. This may adversely affect long-term survival. In a study in which most patients received gemcitabine-based adjuvant treatment, median recurrence-free survival was found to be 22 months in patients who completed adjuvant therapy, and 9 months in patients whose therapy was discontinued early [20]. In our study, almost all patients (92.3%) had adverse events at any grade with mFolfirinox. Most of these were manageable adverse events. However, we would like to emphasize that 2% of patients (one patient) died of treatment-related adverse event in the mFolfirinox group. Therefore, patient selection for the mFolfirinox regimen in the adjuvant treatment of pancreatic cancer is very important. Treatment may be beneficial in patients who can tolerate treatment and experience minimal treatment toxicity.

We would like to highlight a few limitations of our study. The most important limitation is the retrospective nature of our study, and its natural consequences. The uneven distribution between groups and the potential selection bias were the result of this limitation. Second, adverse events may have been underestimated because the data were obtained from hospital records and patient files. Third, there was no granulocyte colony-

stimulating factor usage information available. Fourth, the treatment information at the time of recurrence of the patients was unknown. And finally, genetic factors (microsatellite instability and Breast cancer gene 1-2) that may affect the prognosis of patients were not known.

In conclusion, in the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit. The mFolfirinox regimen was found to be more toxic than other adjuvant regimens, and mFolfirinox regimen should be considered in fit patients.

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