JBUON 2021; 26(6): 2496-2504
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Combination of gemcitabine, infusional 5-fluorouracil and high-dose folinic acid (GEMFUFOL) as adjuvant chemotherapy in resected pancreatic cancer

Ilkay Tugba Unek[1], Ilhan Oztop[1], Dogan Koca[2], Tarkan Unek[3], Anil Aysal Agalar[4], Zeynep Gulsum Guc[1], Sinan Unal[1], Zumre Arican Alicikus[5], Asim Leblebici[6], Hulya Ellidokuz[7], Ozgul Sagol[4], Ugur Yilmaz[8]

[1]Department of Medical Oncology, Dokuz Eylul University School of Medicine, Izmir, Turkey. [2]Department of Medical Oncology, Medical Park Hospital, Kocaeli, Turkey. [3]Department of General Surgery, Dokuz Eylul University School of Medicine, Izmir, Turkey. [4]Department of Pathology, Dokuz Eylul University School of Medicine, Izmir, Turkey. [5]Department of Radiation Oncology, Dokuz Eylul University School of Medicine, Izmir, Turkey. [6]Department of Translational Oncology, Dokuz Eylul University, Institute of Health Sciences, Izmir, Turkey. [7]Department of Preventive Oncology, Dokuz Eylul University, Institute of Oncology, Izmir, Turkey. [8]Department of Medical Oncology, Medical Park Hospital, Izmir, Turkey.

Summary

Purpose: *There are many studies about the administration of gemcitabine and 5-fluorouracil combination regimen for advanced-stage pancreatic ductal adenocarcinoma (PDAC), but no study exists about early-stage PDAC. This study, for the first time, aimed to evaluate the efficacy and tolerability of gemcitabine and infusional 5-fluorouracil with high-dose folinic acid as adjuvant chemotherapy after curative surgery for PDAC.*

Methods: *Patients with curatively resected PDAC were treated with gemcitabine combined with infusional 5-fluorouracil and high-dose folinic acid (GEMFUFOL). This combination regimen was repeated every 2 weeks.*

Results: *A total of 62 patients who received GEMFUFOL as adjuvant chemotherapy were included in this study. At a median follow-up of 16.9 months (range, 3.6-149.2), median disease-free survival (DFS) was 11.8 months (95% CI, 7.9-15.6), with 1-year, 2-year and 3-year DFS rates of 49%, 15% and 11% identified. Median overall survival (OS) was 17.3 months (95% CI, 12.4-22.1) with 1-year, 2-year and 3-year OS rates of 72%, 37% and 17%. Severe toxicity was rarely observed. Two patients (3.2%) developed grade 4 neutropenia; however, febrile neutropenia was observed in 1 patient (1.6%). Three patients (4.8%) had grade 3 neutropenia, 2 patients (3.2%) had grade 3 anemia, 3 patients (4.8%) had grade 3 nausea, 1 patient (1.6%) had grade 3 diarrhea and 1 patient (1.6%) had grade 3 infection.*

Conclusions: *The GEMFUFOL regimen is an effective and tolerable regimen for adjuvant treatment of PDAC and may be an appropriate alternative for patients unsuitable for current standard treatments.*

Key words: *adjuvant chemotherapy, gemcitabine, 5-fluorouracil, folinic acid, pancreatic cancer*

Introduction

ThPancreatic ductal adenocarcinoma (PDAC) is 3rd in the list of cancers causing cancer-related mortality in western countries. Adjuvant chemotherapy administered after curative surgery can significantly increase disease-free survival (DFS) and overall survival (OS) [1,2]. Current and standard adjuvant treatment for PDAC is combination chemotherapy including folinic acid (FA), 5-fluorouracil

Corresponding author: Ilkay Tugba Unek, MD. Dokuz Eylul University School of Medicine, Department of Medical Oncology, 35340, Balcova, Izmir, Turkey.
Tel: +90 2324124801; Fax: +90 2322789495; Email: ilkaytugbaunek@gmail.com
Received: 17/08/2021; Accepted: 05/09/2021

(5-FU), irinotecan and oxaliplatin [FOLFIRINOX] for 6 months, while patients unsuit to this chemotherapy regimen receive combination chemotherapy including gemcitabine and capecitabine (GemCap) for 6 months [1-4]. Adjuvant chemoradiation may be recommended to patients with microscopically positive margins (R1) and/or lymph node (LN) positive disease after completion of 4-6 months of systemic adjuvant chemotherapy [3,4].

Recently, in the multicenter, randomized PRODIGE 24/CCTG PA.6 study, 493 patients with resected PDAC, aged <80 years, and with Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, were randomized into two groups as modified-FOLFIRINOX (mFOLFIRINOX) regimen and gemcitabine monotherapy. The results of the study identified median DFS as 21.6 months in the mFOLFIRINOX group and 12.8 months in the gemcitabine monotherapy group (p<0.001), while median OS was 54.4 months in the mFOLFIRINOX group and 35.0 months in the gemcitabine monotherapy group (p=0.003) [5]. Based on efficacy data for the GemCap combination regimen for advanced stage PDAC [6,7], the European Study Group for Pancreatic Cancer (ESPAC)-4 study randomized 730 patients with resected PDAC into two groups as GemCap combination regimen and gemcitabine monotherapy. The GemCap combination was identified to have longer median DFS (13.9 months vs. 13.1 months, p=0.082) and longer median OS (28.0 months vs. 25.5 months, p=0.032) compared to gemcitabine monotherapy [8]. In these studies, mFOLFIRINOX and GemCap combination regimes were shown to have superior survival outcomes compared to gemcitabine monotherapy and are recommended as the standard treatment for adjuvant therapy for PDAC. Patients unsuitable for these combination regimens or with ECOG performance score of 2, are recommended to receive single-agent gemcitabine or bolus 5-FU/FA [1-4]. Single-agent gemcitabine and bolus 5-FU/FA took their places in PDAC adjuvant therapy guidelines with the Charité Onkologie (CONKO)-001 study and the ESPAC-3 study, respectively [9,10].

As 5-FU and gemcitabine have synergistic effects and do not have overlapping toxicity profiles, the 5-FU and gemcitabine combination is included among ideal chemotherapy combination regimens [11-12]. There are many studies about administration of the gemcitabine and 5-FU combination regimen for advanced stage PDAC [13-19], but no study was found about early-stage PDAC. This study, for the first time, aimed to evaluate the efficacy and tolerability of gemcitabine combined with infusional 5-FU and high-dose FA (GEMFUFOL) as adjuvant chemotherapy after curative surgery for PDAC.

Methods

Patients and study design

Between 2000-2019, a total of 62 patients who received GEMFUFOL as adjuvant chemotherapy after curative surgery for PDAC at the Medical Oncology Department of the Dokuz Eylul University Faculty of Medicine were included in this study. The medical records of these patients were retrospectively reviewed. Inclusion criteria for the study were ECOG performance score ≤2, age 18 years or older and sufficient hematological (leukocytes >4000/mm^3, neutrophils >1500/ mm^3, platelets >100.000/ mm^3, hemoglobin level ≥10 g/dL), renal (creatinine clearance >50 ml/min) and hepatic (serum total bilirubin level ≤1.5 times the upper limit of the normal range) functions. Patients with macroscopic residue (R2 resection), tumour-node-metastasis (TNM) stage 4, previous history of chemotherapy and radiotherapy, symptomatic heart failure or coronary artery disease were excluded from the study. Pathologic stage of patients was updated according to the new staging system [American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)] by a pathologist, as the TNM staging for pancreatic cancer changed during the study period.

Treatment regimen

Each 2-week cycle consisted of gemcitabine 1000 mg/m^2, 30-min iv infusion on day 1, FA 200 mg/m2 as 2-h iv infusion followed by 5-FU 400 mg/m2 iv bolus and 5-FU 600 mg/m2 continuous 22-h iv infusion on days 1 and 2 (first 8 patients) and gemcitabine 1250 mg/m2, 30-min iv infusion plus FA 400 mg/m2 as 2-h iv infusion followed by 5-FU 400 mg/m2 iv bolus on day 1 and 5-FU 2400 mg/m2 continuous 46-h iv infusion (next 54 patients). Routine prophylactic granulocyte-colony stimulating factor (G-CSF) was not used. Postoperative 4-6 months of systemic adjuvant chemotherapy was planned. Patients considered to have indications underwent adjuvant chemoradiotherapy. Chemoradiotherapy consisted of 45 Gy of radiation at 1,8 Gy per day with concurrent infusion of 5-FU or gemcitabine. All patients were informed about the treatment and signed the informed consent form.

Assessment of efficacy and toxicity

DFS was defined as the period from the date of initial chemotherapy to the date of disease recurrence, while OS was defined as the period from the date of initial chemotherapy to the patient's last visit or date of death. At the beginning of each cycle, the status of patients was assessed by means of a review of systems, physical examination, complete blood counts, and serum biochemical tests.

Imaging studies were documented by computed tomography at baseline and every 3 months. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistics

Statistical analyses were carried out using the SPSS 22.0 software. The patient survival was evaluated by the Kaplan-Meier method. P values<0.05 was considered to indicate statistical significance. Multivariate analysis was made using Cox regression analysis.

Results

Patients

The study included 62 patients who received GEMFUFOL as adjuvant chemotherapy after curative surgery for PDAC. The demographic and disease characteristics of the patients at baseline are shown in Table 1. Of the patients, 58.1% were male and median age was 60.5 years (range, 29-75). Among the most commonly observed comorbidities were 32.3% diabetes mellitus and 22.6% hypertension. Forty-eight patients (77.4%) had good performance status (ECOG 0-1), while the remaining 14 patients (22.6%) had low performance status (ECOG 2). Primary tumor was localized to the head of the pancreas in 88.7% of the patients. Pancreaticoduodenectomy (Whipple) was performed in 80.6% of the patients. Six patients (9.7%) had distal pancreaticoduodenectomy and 6 patients (9.7%) had total pancreaticoduodenectomy. Median tumour diameter was identified as 3.3 cm (range, 0.7-9.0). In 87.1% of the patients, tumour was >2 cm and 82.3% had at least 1 lymph-node (LN) metastasis. Twenty-nine patients (46.8%) had an R1 status defined by microscopic tumour cells within 1 mm of the resection margin. Of the patients, 41.9% had stage 2B and nearly half (43.6%) had stage 3. In 95.2% of the patients there was perineural invasion, 83.9% had LN invasion and 74.2% had vascular invasion identified.

Treatment delivery

Five hundred and twelve cycles of chemotherapy were administered with a median of 8 cycles ranging from 2 to 12 cycles. Fourty-four (70.9%) patients were also treated with concurrent chemoradiotherapy. The proportion completing the planned treatment was 66.1%. Of the 21 patients who did not complete treatment, 19 stopped due to disease progression (90.5%) and 2 due to grade 3-4 toxicity (9.5%).

Efficacy and survival

The median follow-up time was 16.9 months (range, 3.6-149.2). During follow-up, 49 patients (79%) developed local recurrence and/or distant metastasis. Of the patients with recurrence, 57.1% had recurrence in the lymph nodes, 42.9% in the

Table 1. Baseline characteristics of patients

Characteristics	*n (%)*
Gender	
Male	36 (58.1)
Female	26 (41.9)
Age, median (range)	60.5 (29-75)
Comorbidity	
DM	20 (32.3)
HT	14 (22.6)
Others	8 (12.9)
ECOG* performance score	
0-1	48 (77.4)
2	14 (22.6)
Surgery	
Pancreaticoduodenectomy (Whipple)	50 (80.6)
Distal pancreatectomy	6 (9.7)
Total pancreaticoduodenectomy	6 (9.7)
Maximum tumor diameter (cm), median (range)	3.3 (0.7-9.0)
Tumour in greatest dimension (cm)	
Tumour ≤2	8 (12.9)
Tumour >2 cm and ≤4	40 (64.5)
Tumour >4	14 (22.6)
Invasion to major vascular structure (T4)	4 (6.5)
Lymph node (LN) involvement	
LN negative	11 (17.7)
1-3 LN positive	29 (46.8)
≥ 4 LN positive	22 (35.5)
Stage†	
1A (T1N0)	3 (4.8)
1B (T2N0)	5 (8.1)
2A (T3N0)	1 (1.6)
2B (T1-3,N1)	26 (41.9)
3 (T1-3,N2) (T4, Any N)	27 (43.6)
Site of tumour	
Head of pancreas	55 (88.7)
Body/tail of pancreas	7 (11.3)
Histologic differentiation	
Well differentiated	33 (53.2)
Moderately differentiated	24 (38.7)
Poorly differentiated	5 (8.1)
Surgical margin	
Negative (R0)	33 (53.2)
Positive (R1)	29 (46.8)
Perineural invasion	59 (95.2)
Lymphatic invasion	52 (83.9)
Vascular invasion	46 (74.2)

*Eastern Cooperative Oncology Group, †Stages according to the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017).

liver, 34.7% in the peritoneum, 32.7% in the lungs and 30.6% had local recurrence. In 36 of the 49 patients with recurrence (73.5%), palliative chemotherapy was applied. At the end of the study, 7 patients were alive and 6 of them were disease-free.

Median DFS was 11.8 months (95% CI, 7.9-15.6), with 1-year, 2-year and 3-year DFS rates of 49%, 15% and 11% (Figure 1). Median OS was 17.3 months (95% CI, 12.4-22.1) with 1-year, 2-year and 3-year OS rates of 72%, 37% and 17% (Figure 2). Table 2 shows univariate analysis of clinical and pathologic factors for OS. In patients with ECOG performance score 0-1, median OS was 22.6 months, while in patients with ECOG performance score 2, median OS was 8.1 months, (p<0.001). Median OS was 21.5 months for stage 1 cases, 22.6 months for stage 2 cases and 15.9 months for stage 3 cases (p=0.045). In patients with well-differenti-

Table 2. Univariate analysis for overall survival

Parameters	*Median OS (months)*	*95% Confidence interval (CI)*	*Log-rank p value*
Gender			0.699
Male	17.6	12.32-22.88	
Female	16.2	13.78-18.69	
Age, years			0.314
<60	16.5	5.27-27.66	
≥60	17.3	15.18-19.35	
Comorbidity			0.242
Absent	16.5	8.69-24.24	
Present	17.3	11.63-22.91	
ECOG* performance score			**<0.001**
0-1	22.6	17.02-28.25	
2	8.1	4.07-12.13	
Tumour in greatest dimension, cm			0.444
Tumour ≤2	24.2	7.97-40.50	
Tumour >2 cm and ≤4	19.1	15.14-23.13	
Tumour >4	15.7	11.58-19.89	
Lymph node (LN) involvement			0.177
LN negative	15.7	5.27-26.20	
1-3 LN positive	22.6	18.55-26.72	
≥ 4 LN positive	13.7	9.11-18.23	
Stage†			**0.045**
1	21.5	5.11-37.82	
2	22.6	16.29-28.98	
3	15.9	10.68-21.19	
Histologic differentiation			**0.040**
Well differentiated	24.2	17.73-30.74	
Moderately/Poorly differentiated	13.7	8.75-18.59	
Surgical margin			0.82
Negative (R0)	16.2	12.60-19.87	
Positive (R1)	17.6	11.77-23.43	
Lymph node (LN) invasion			0.340
Negative	21.5	9.07-33.86	
Positive	17.2	15.41-19.06	
Vascular invasion			0.507
Negative	21.5	6.80-36.13	
Positive	17.2	15.45-19.01	

*Eastern Cooperative Oncology Group, †Stages according to the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017). Bold numbers denote statistical significance.

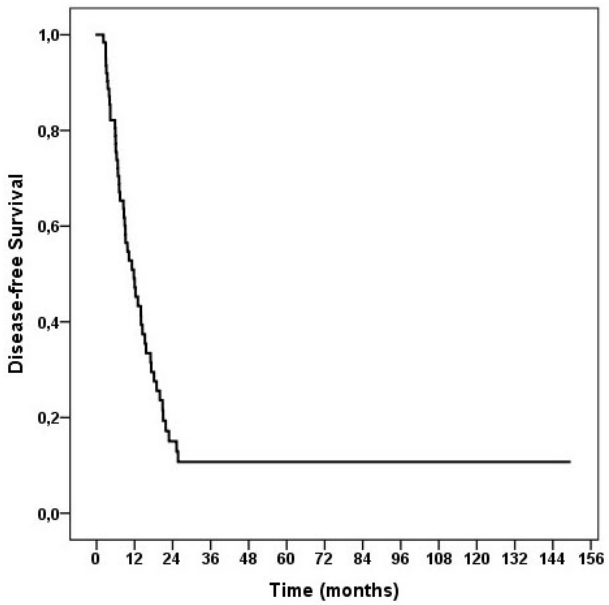

Figure 1. Disease-free survival of all patients.

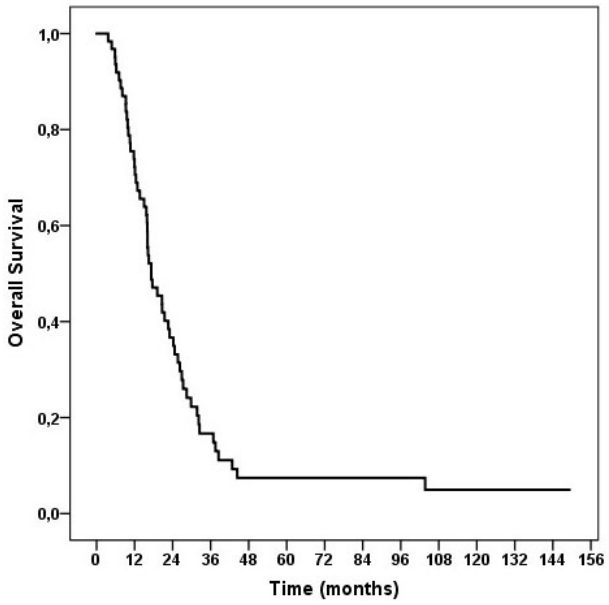

Figure 2. Overall survival of all patients.

Table 3. Multivariate analysis for overall survival

Parameters	*Coefficient β*	*SE*	*p value*	*Odds ratio*	*95% CI*
ECOG* performance score	1.493	0.422	<0.001	4.452	1.948-10.172
Stage	1.129	0.567	0.046	3.094	1.019 - 9.395
Histologic differentiation	0.925	0.326	0.005	2.522	1.330-4.782

*Eastern Cooperative Oncology Group

Table 4. Toxicities associated with chemotherapy

Toxicity	*Grades*	
	Grade I-II n(%)	*Grade III-IV n(%)*
Anemia	30 (48.4)	2 (3.2)
Neutropenia	15 (24.2)	5 (8.1)
Thrombocytopenia	6 (9.7)	-
Nausea/vomiting	11 (17.7)	3 (4.8)
Diarrhea	6 (9.7)	1 (1.6)
Constipation	2 (3.2)	-
Oral mucositis	2 (3.2)	-
Infection	13 (20.9)	1 (1.6)
Hepatic	9 (14.5)	-
Renal	2 (3.2)	-
Skin	4 (6.5)	-

ated tumour, median OS was 24.2 months, while, in patients with moderately/poorly differentiated tumour, median OS was 13.7 months, (p=0.040). By multivariate analysis, ECOG performance score, tumour stage, and histologic differentiation were found to be independently associated with OS (p<0.05, Table 3).

Toxicity

Severe toxicity was rarely observed after adjuvant chemotherapy was administered to patients. Two patients (3.2%) developed grade 4 neutropenia; however, febrile neutropenia was observed in 1 patient (1.6%). Three patients (4.8%) had grade 3 neutropenia, 2 patients (3.2%) had grade 3 anemia, 3 patients (4.8%) had grade 3 nausea, 1 patient (1.6%) had grade 3 diarrhea and 1 patient (1.6%) had grade 3 infection. Due to grade 3-4 toxicity, 5 patients (8.1%) had dose reduction of all drugs by 25%. Chemotherapy-associated toxicities are shown in Table 4.

Discussion

This retrospective study evaluated the efficacy and tolerability of the GEMFUFOL regimen as adjuvant chemotherapy in 62 patients with resected PDAC for the first time in the literature. In our study, median DFS was 11.8 months, while median OS was 17.3 months. This chemotherapy regimen was well tolerated and identified to have low rates of toxicity.

Considering that the longest survival to date for patients with resected PDAC was obtained

with the mFOLFIRINOX regimen, this regimen should be administered to all appropriate patients. However, in order to administer mFOLFIRINOX, patients should have good performance status level, and no history of chronic diarrhea, diabetic polyneuropathy or severe heart disease [1,2]. For patients aged >70 years median DFS did not reach statistically significant difference between the mFOLFIRINOX and the gemcitabine [5], and therefore it is considered that administration of the mFOLFIRINOX regimen is more appropriate for patients <70 years of age. Long survival was obtained with the mFOLFIRINOX regimen; however, the majority of patients (75.9%) were observed to have grade 3-4 toxicity [5].

In the ESPAC-4 study, the GemCap combination group had median DFS of 13.9 months, while in the CONKO-001 study the gemcitabine group had 13.4 months DFS and in the ESPAC-3 study the bolus 5-FU/FA group had 14.1 months DFS. In our study, the median DFS was close to the median DFS in these phase 3 randomized studies [8-10]. In the GemCap combination, single-agent gemcitabine and bolus 5-FU/FA for adjuvant treatment of PDAC had similar median DFS, but different toxicity profiles [8-10]. The ESPAC-4 study showed more common grade 3-4 neutropenia (38% vs. 24%, p=0.0001), diarrhea (5% vs. 2%, p=0.008) and hand-foot syndrome (7% vs.0%, p<0.0001) for GemCap combination compared to the single-agent gemcitabine [8]. In the ESPAC-3 study, the bolus 5-FU/FA group had more frequent grade 3-4 stomatitis (10% vs. 0%, p≤0.001) and diarrhea (13% vs. 2%, p≤0.001) compared to the gemcitabine group [10]. As it is less toxic than bolus 5-FU/FA administration, single-agent gemcitabine was chosen for adjuvant treatment of PDAC until the publication of the ESPAC-4 study results.

For colorectal cancer patients, the once every 14-day "de Gramont regimen" showed lower toxicity compared to bolus 5-FU/FA regimen and allowed the possibility to administer 2-fold higher 5-FU dose and obtain increased response rates [20,21]. Leukopenia, diarrhea and stomatitis observed with bolus 5-FU/FA administration were observed at lower rates with the "de Gramont regimen" [21]. Similarly, in our study with gemcitabine administered combined with "de Gramont regimen" once every 14 days, grade 3-4 leukopenia (8.1%), diarrhea (1.6%) and anemia (3.2%) were rarely observed, with grade 3-4 stomatitis not reported (Table 4).

Great advances have been recorded for adjuvant treatment of PDAC in the last 10 years. Median OS in phase 3 randomized adjuvant chemotherapy studies was reported as 22.8 months with single-agent gemcitabine in the 2007 CONKO-001 study, 23.0 months with bolus 5-FU/FA in the 2010 ESPAC-3 study, 28.0 months with the GemCap combination in the 2017 ESPAC-4 study and 54.4 months with the mFOLFIRINOX combination in the 2018 PRODIGE24/CCTGPA.6 study [5,8-10]. In our study, median OS was shorter than the median OS reported in phase 3 randomized studies evaluating adjuvant treatment for PDAC. However, a retrospective study evaluating 472 patients with resected PDAC and periampullary adenocarcinoma with adjuvant chemotherapy and/or chemoradiotherapy administered from 2003-2013 in Turkey reported median DFS 12 months and median OS 19 months, similar to our study [22]. In our study, administering the GEMFUFOL regimen from 2000 to 2019, it is considered that our survival results might be affected due to 26.5% of patients developing recurrence, not having palliative chemotherapy administered, the lack of effective chemotherapy regimens for metastatic disease before 2010 (FOLFIRINOX, Nab-paclitaxel+gemcitabine) [23,24], advances in treatment applications (surgery, radiotherapy, palliative treatment, etc.) through the years, and the high percentage of patients (22.6%) with ECOG performance score 2.

In a study of adjuvant gemcitabine, administered once every 14 days as in our study but as a single-agent, median DFS was 12.5 months, with median OS 20.2 months with nearly all patients (93%) administered gemcitabine completing the planned treatment [25]. This study which was conducted by Toyama et al identified similar median DFS and OS in patients administered the standard weekly gemcitabine in the CONKO-001 study. In the CONKO-001 study, considering only 62% of patients administered gemcitabine completed treatment, administration of gemcitabine once every two weeks is considered to be as effective and more tolerable than weekly gemcitabine administration. Similar to the CONKO-001 study, in the ESPAC-4 study only 65% of those receiving single-agent gemcitabine and 54% of those receiving GemCap completed treatment [8]. In our study, 66.1% of patients completed the planned treatment. Of the 21 patients who did not complete treatment, 19 stopped due to disease progression (90.5%) and 2 due to grade 3-4 toxicity (9.5%).

The chemotherapy dose intensity and cumulative dose in adjuvant treatment for PDAC are associated with survival [26-28]. As a result, in terms of leukopenia/neutropenia requiring reduced/delayed/cancelled chemotherapy doses, G-CSF prophylaxis becomes important. With si-

multaneous administration of cytotoxic agents like capecitabine with G-CSF, the use of G-CSF is known to increase the proliferative activity in bone marrow and increase myelotoxicity of chemotherapy. Considering rapidly dividing and immature myeloid cells are very susceptible to cytotoxic chemotherapy, G-CSF use is not recommended in the period from 24 h before chemotherapy to 24 h after chemotherapy [29,30]. In the literature, there are very few studies about simultaneous administration of capecitabine and G-CSF [31-34]. In the ESPAC-4 study with 38% rates of grade 3-4 neutropenia in the GemCap combination group, there was no information reported about the use of G-CSF [8]. As a result, there is a need for clinical studies evaluating the efficacy and reliability of G-CSF primary and secondary prophylaxis for patients using capecitabine. Compared with the GemCap combination, the GEMFUFOL regimen is suitable for G-CSF prophylaxis. In a GEMFUFOL regimen once every 14 days, after 5-FU 46-h infusion is completed, G-CSF may be administered 24-48 h later. In our study, grade 3-4 neutropenia was 8.1% and G-CSF prophylaxis was administered to these patients.

Toxicity frequently observed and making treatment compliance difficult with oral capecitabine (hand-foot syndrome, leukopenia and diarrhea) is reported at lower rates with the "de Gramont regimen". A review comparing the "de Gramont regimen" and oral capecitabine in patients with metastatic colorectal cancer patients, revealed that the two treatments had similar efficacy; however, side effects of oral capecitabine were greater (grade 3 hand-foot syndrome 17% vs. 1%, grade 3-4 leukopenia 37% vs. 1%, diarrhea 13% vs. 5%) [35]. In our study, combining gemcitabine with the "de Gramont regimen", hand-foot syndrome was not observed, and grade 3-4 leukopenia (8.1%) and grade 3-4 diarrhea (1.6%) rarely developed.

The disadvantage of the GEMFUFOL regimen is that it requires a central venous catheter for infusion of 5-FU. The 5-FU prodrug of capecitabine has the advantage of oral administration; however, compliance with oral treatment may be difficult for patients who have undergone pancreatic surgery. After standard pancreaticoduodenectomy (Whipple), patients may develop gastrointestinal symptoms linked to surgery. Delayed gastric emptying, reduced pancreatic exocrine functions, reduced food grinding in patients with partial stomach resection in the Whipple operation, reduced secretion of secretin and cholecystokinin linked to duodenectomy and jejunal reconstruction cause the development of maldigestion, malabsorption and gastrojejunal anastomotic ulcers. As a result, indigestion, bloating, gas, diarrhea and weight loss may occur in patients. In the postoperative period, oral tablets containing pancreas enzymes for pancreatic exocrine insufficiency are recommended along with proton pump inhibitors (PPI) for anastomotic ulcer prophylaxis. The PPI treatment recommended for ulcer prophylaxis at the same time ensures formation of the necessary alkali environment required for absorption of pancreatic enzyme supplements [36].

There is conflicting information about the interaction between PPI and capecitabine. Preclinical studies suggested that there was no interaction [37], but in recent retrospective studies, simultaneous use of capecitabine with PPI was identified to reduce the efficacy of capecitabine [38-40]. In the commonly used medication interaction databases of Lexicomp® and Micromedex®, the present of interaction between capecitabine and PPI was added based on these studies [41,42]. Micromedex® recommends stopping PPI treatment or exchanging capecitabine with infusion 5-FU due to the capecitabine-PPI interaction [42]. Similarly, in a systematic review, it is recommended to avoid overuse and misuse of PPI in cancer patients using capecitabine [43].

As compliance with oral capecitabine treatment may be hard to link to gastrointestinal symptoms developing after Whipple, considering the majority of patients require PPI use after Whipple, and that simultaneous use of PPI with capecitabine reduces the efficacy of capecitabine, the GEMFUFOL regimen assessed in our study is considered to be an appropriate treatment alternative for adjuvant treatment of PDAC.

In conclusion, the GEMFUFOL regimen is an effective and tolerable regimen for adjuvant treatment of PDAC and may be an appropriate alternative for patients unsuitable for FOLFIRINOX and GemCap combination treatments. Due to its efficacy and low toxicity profile compared to current standard treatments, there is a need for randomized phase 3 studies to research the GEMFUFOL regimen.

Ethics approval

This study was approved by the local ethics committee of the Dokuz Eylul University, Izmir, Turkey (No.2020/08-27).

Conflict of interests

The authors declare no conflict of interests.

References

1. Springfeld C, Jäger D, Büchler MW et al. Chemotherapy for pancreatic cancer. Presse Med 2019;48(3 Pt 2):e159-e174.
2. Klaiber U, Hackert T, Neoptolemos JP. Adjuvant treatment for pancreatic cancer. Transl Gastroenterol Hepatol 2019;4:27.
3. Khorana AA, McKernin SE, Berlin J et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. J Clin Oncol 2019;37:2082-8.
4. Yegya-Raman N, Shah MM, Grandhi MS et al. Adjuvant therapeutic strategies for resectable pancreatic adenocarcinoma. Ann Pancreat Cancer 2018;1:20.
5. Conroy T, Hammel P, Hebbar M et al; Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395-2406.
6. Herrmann R, Bodoky G, Ruhstaller T et al; Swiss Group for Clinical Cancer Research; Central European Cooperative Oncology Group. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007;25:2212-2217.
7. Cunningham D, Chau I, Stocken DD et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009;27:5513-8.
8. Neoptolemos JP, Palmer DH, Ghaneh P et al; European study group for pancreatic cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017;389:1011-24.
9. Oettle H, Neuhaus P, Hochhaus A et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA 2013;310:1473-81.
10. Neoptolemos JP, Stocken DD, Bassi C et al; European study group for pancreatic cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-81.
11. Di Marco M, Di Cicilia R, Macchini M et al. Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review). Oncol Rep 2010;23:1183-92.
12. Oettle H, Riess H. Gemcitabine in combination with 5-fluorouracil with or without folinic acid in the treatment of pancreatic cancer. Cancer 2002;95(4 Suppl):912-22.
13. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern cooperative oncology group trial E2297. J Clin Oncol 2002;20:3270-5.
14. Di Costanzo F, Carlini P, Doni L et al. Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). Br J Cancer 2005;93:185-9.
15. Choi JH, Ahn MJ, Im SA et al. Gemcitabine and infusional 5-fluorouracil in advanced pancreatic cancer: a clinical benefit response-oriented phase II study. Cancer Res Treat 2003;35:213-7.
16. Shiah HS, Cheng AL, Hsu C et al. Phase I-II trial of weekly gemcitabine plus high-dose 5-fluorouracil and leucovorin in advanced pancreatic cancer. J Gastroenterol Hepatol 2006;21:531-6.
17. Louvet C, André T, Hammel P et al. Phase II trial of bimonthly leucovorin, 5-fluorouracil and gemcitabine for advanced pancreatic adenocarcinoma (FOLFUGEM). Ann Oncol 2001;12:675-9.
18. André T, Noirclerc M, Hammel P et al. GERCOR: Phase II study of leucovorin, 5-fluorouracil and gemcitabine for locally advanced and metastatic pancreatic cancer (FOLFUGEM 2). Gastroenterol Clin Biol 2004;28:645-50.
19. Oztop I, Alacacioglu A, Unek IT et al. Gemcitabine plus infusional 5-fluorouracil and high dose leucovorin in advanced stage pancreatic cancer. JBUON 2010;15:462-9.
20. Beerblock K, Rinaldi Y, André T et al. Bimonthly high dose leucovorin and 5-fluorouracil 48-hour continuous infusion in patients with advanced colorectal carcinoma. Groupe d'Etude et de Recherche surles Cancers de l'Ovaire et Digestifs (GERCOD). Cancer 1997;79:1100-5.
21. de Gramont A, Bosset JF, Milan C et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 1997;15:808-15.
22. Turan N, Benekli M, Unal OU et al; Anatolian Society of Medical Oncology (ASMO). Impact of adjuvant treatment modalities on survival outcomes in curatively resected pancreatic and periampullary adenocarcinoma. Chin J Cancer Res 2015;27:408-16.
23. 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;364:1817-25.
24. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
25. Toyama Y, Yoshida S, Saito R et al. Successful adjuvant bi-weekly gemcitabine chemotherapy for pancreatic cancer without impairing patients' quality of life. World J Surg Oncol 2013;11:3.
26. Valle JW, Palmer D, Jackson R et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol 2014;32:504-12.
27. Matsumoto I, Tanaka M, Shirakawa S et al. Postoperative serum albumin level is a marker of incomplete adjuvant chemotherapy in patients with pancreatic ductal adenocarcinoma. Ann Surg Oncol 2015;22:2408-15.

28. Yabusaki N, Fujii T, Yamada S et al. The significance of relative dose intensity in adjuvant chemotherapy of pancreatic ductal adenocarcinoma-including the analysis of clinicopathological factors influencing relative dose intensity. Medicine (Baltimore) 2016;95:e4282.
29. Granocyte (lenograstim) [summary of product characteristics]. Turnham Green, London, UK: Chugai Pharma UK Limited; April 2015.
30. Lonquex (lipegfilgrastim) [summary of product characteristics]. Harlow, Essex, UK: Teva Pharma BV; June 2015.
31. Wenzel C, Bartsch R, Locker GJ et al. Preoperative chemotherapy with epidoxorubicin, docetaxel and capecitabine plus pegfilgrastim in patients with primary breast cancer. Anticancer Drugs 2005;16:441-5.
32. Polyzos A, Felekouras E, Karatzas T et al. Modified docetaxel-cisplatin in combination with capecitabine as first-line treatment in metastatic gastric cancer. a phase II study. Anticancer Res 2012;32:4151-6.
33. Natoli C, Cianchetti E, Tinari N et al. A phase II study of dose-dense epirubicin plus cyclophosphamide followed by docetaxel plus capecitabine and pegfilgrastim support as preoperative therapy for patients with stage II, IIIA breast cancer. Ann Oncol 2007;18:1015-20.
34. Becerra CR, Verma UN, Tran HT, Tavana D, Williams NS, Frenkel EP. Phase I dose escalation study with irinotecan, capecitabine, epirubicin, and granulocyte colony-stimulating factor support for patients with solid malignancies. Am J Clin Oncol 2008;31:219-25.
35. Saif MW. Capecitabine versus continuous-infusion 5-fluorouracil for colorectal cancer: a retrospective efficacy and safety comparison. Clin Colorectal Cancer 2005;5:89-100.
36. Tran TC, van Lanschot JJ, Bruno MJ, van Eijck CH. Functional changes after pancreatoduodenectomy: diagnosis and treatment. Pancreatology 2009;9:729-37.
37. Cheng V, Lemos M, Hunter N, Badry N, Lemos J. Concomitant use of capecitabine and proton pump inhibitors - Is it safe? J Oncol Pharm Pract 2019;25: 1705-11.
38. Sun J, Ilich AI, Kim CA et al. Concomitant administration of proton pump inhibitors and capecitabine is associated with increased recurrence risk in early stage colorectal cancer patients. Clin Colorectal Cancer 2016;15:257-63.
39. Wong GG, Ha V, Chu MP et al. Effects of proton pump inhibitors on FOLFOX and CapeOx regimens in colorectal cancer. Clin Colorectal Cancer 2019;18:72-9.
40. Chu MP, Hecht JR, Slamon D et al. Association of proton pump inhibitors and capecitabine efficacy in advanced gastroesophageal cancer: secondary analysis of the TRIO-013/LOGiC randomized clinical trial. JAMA Oncol 2017;3:767-73.
41. Lexicomp Online®: interactions (database on the Internet). Lexi-Comp Inc. http://online.lexi.com. Accessed 3 Nov 2020.
42. MICROMEDEX® 2.0 Drug Interactions (database on the Internet). Truven Health Analytics, updated periodically. https://www.micromedexsolutions.com. Accessed 3 Nov 2020.
43. Viñal D, Rodriguez-Salas N, Perez-Wert P, Higuera O, Ghanem I, Feliu J. Efficacy of capecitabine when used concomitantly with proton pump inhibitors in cancer patients: a systematic review. Clin Transl Oncol 2020;22:1288-94.