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Original Article

The evaluation of efficacy and tolerability of gemcitabine vs. capecitabine therapy in the second-line setting for metastatic pancreatic cancer patients with poor performance status

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy and tolerability of single-agent gemcitabine vs. capecitabine therapy in the second-line setting for metastatic Pancreatic Cancer (mPC) patients with poor performance status.

Material and methods: A total of 48 patients with mPC, who were followed and treated in oncology center between 2012 and 2017, were included. After a failure of first-line therapy, patients with an ECOG-PS 2 treated with capecitabine or gemcitabine monotherapy in the secondline setting were retrospectively analyzed.

Results: Of the 48 patients, 26(54.2%) were males and 22(45.8%) were females. The median age of the patients was 62 years(range, 31-82). Treatment regimens in the first-line setting were as follows; gemcitabine+cisplatin in 24(50%) patients, gemcitabine+nub-paclitaxel in 4(8.3%) patients, FOLFIRINOX in 8(16.7%) patients, FOLFOX in 8(16.7%) patients, and gemcitabine+oxaliplatine in 4(8.3%) patients. After progression on first-line therapy, 29(60.5%) patients were treated with capecitabine in the second-line setting, while 19(39.5%) patients were given gemcitabine. Median progression-free survival was found to be 4 months(95% CI,1.9-6.0) in patients receiving capecitabine compared to 2 months(95% CI, 0.5-3.4) in those treated with gemcitabine (p=0.271). Median overall survival was 6.0 months(95% CI, 2.0-9.9) in patients receiving capecitabine therapy versus 5.0 months (95% CI, 1.0-8.9) in those treated with gemcitabine monotherapy (p=0.353).

Conclusions: Optimal second-line treatment for mPC has not yet been established. In the present study, capecitabine monotherapy was compared to gemcitabine and it was found that they both had similar efficacy in the second-line treatment for mPC patients who were not eligible for combination chemotherapy regimen.

1. Introduction

The majority of exocrine pancreatic cancers (85%) are adenocarcinomas originating from the ductal epithelium. Pancreatic cancer is one of the most aggressive, lethal, and malignant cancers which occur more frequently in advanced ages (40–85 years), with an increasing frequency in recent years. In the United States, approximately 56,770 people develop exocrine pancreatic cancer for each year, with most of the patients ultimately dying from this disease due to its aggressive character.[1,2]

Surgical resection is the only potential curative treatment modality. However, only 15%–20% of patients are candidates for surgery. The incidence rates of pancreatic cancer are approximately equal for males and females. Survival rate for metastatic Pancreatic Cancer (mPC) is extremely poor, with 5-year survival rates being around 2%. So far, various classes of chemotherapy agents have been used to prolong survival of patients with mPC.[2,3]

Chemotherapy is a plausible option for patients with

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unresectable or advanced-stage disease and has been shown to prolong survival rates when compared to Best Supportive Care (BSC). While gemcitabine was the only preferred agent in first-line treatment until 2011, subsequent studies have revealed that 5-fluorouracil (5-FU) + Leucovorin (LV) + Irinotecan + Oxaliplatine (FOLFIRINOX) combination regimen was superior to single agent gemcitabine. In addition, nab-paclitaxel + gemcitabine combination was shown to be superior to gemcitabine alone in the first-line setting.[3–5]

The optimal second-line treatment option for mPC has not been established yet, hence decision for second-line therapy is usually depends on the regimens used in the first-line setting, patient's performance status, and biliary function status.[6] Clinical studies do not include patients with poor performance status; hence, there is no optimal treatment guideline for the second-line setting of these patients.

Herein we aimed to evaluate the efficacy and tolerability of single-agent gemcitabine vs. capecitabine in mPC patients with poor performance status.

2. Materials and methods

2.1. Patients

The study included mPC patients who were followed and treated in oncology clinic between 2012 and 2017. The exclusion criteria were as follows; patients with a second primary malignancy, those with no evidence of metastatic disease at the time of diagnosis, age <18 years, patients treated with combination regimen in the second-line setting, and those with incomplete data. Patients with advanced-stage disease progressing on first-line therapy who had ECOG-PS score of 2 before the initiation of second-line therapy were included in the study.

2.2. Data collection

The data regarding patient and disease characteristics including gender, age, ECOG-PS, smoking status, presence of comorbid disease (diabetes, hypertension, e.g.), site of metastasis at initial diagnosis, treatment regimens used in first-, second-, and third-line setting, number of chemotherapy cycles, grade 3–4 side effects, and patients' final status were obtained from the written archive

Table 1
Patient Data.

		All patients (n = 48)		Capecitabine (n = 29)		Gemcitabine (n = 19)		
		n	%	n	%	n	%	p
Gender	Male	26	54.2	16	55.2	10	52.6	0.548
	Female	22	45.8	13	44.8	9	47.4	
Age (Years)	median (range)	62 (31–82)		65 (34–80)		53 (31–82)		0.068
Smoking Status	No	24	51.1	16	55.2	8	44.4	0.556
	Yes	23	48.9	13	44.8	10	55.6	
Diabetes mellitus	No	35	74.5	19	65.5	16	88.9	0.072
	Yes	12	25.5	10	34.5	2	11.1	
Hypertension	No	38	79.2	20	69.0	18	94.7	0.065
	Yes	10	20.8	9	31.0	1	5.3	0.065
The site of metastasis at diagnosis	Liver	46	95.8	27	93.1	19	100.0	0.512
	Peritoneum	10	20.8	8	27.6	2	10.5	0.144
	Lung	3	6.3	3	10.3	0	0.0	0.211
	Distant LN	2	4.2	1	3.4	1	5.3	0.640
	Bone	2	4.2	0	0.0	2	10.5	0.152
	Brain	1	2.1	0	0.0	1	5.3	0.396
First-line therapy	Cisplatin + gemcitabine	24	50.0	20	69.0	4	21.1	**<0.001**
	Gemcitabine+ nab-paclitaxel	4	8.3	4	13.8	0	0.0	
	FOLFIRINOX	8	16.7	0	0.0	8	42.1	
	FOLFOX	8	16.7	2	6.9	6	31.6	
	GEMOX	4	8.3	3	10.3	1	5.3	
Number of cycles in second-line	Mean ± SD	4.1 ± 2		4.5 ± 2.0		3.7 ± 1.8		0.367
Response to second-line therapy	PR	9	18.8	6	20.7	3	15.8	0.716
	SD	10	20.8	7	24.1	3	15.8	
	PD	29	60.4	16	55.2	13	68.4	
Toxicity profile (Grade3-4)	None	38	79.2	24	82.8	14	73.7	**0.013**
	hand-foot syndrome	4	8.3	4	13.8	0	0	
	Thrombocytopenia	4	8.3	0	0	4	21.1	
	Anemia	2	4.2	1	3.4	1	5.3	
Third-line therapy	No	44	91.7	26	89.7	18	94.7	0.479
	Yes	4	8.3	3	10.3	1	5.3	
Last status	Dead	46	95.8	28	96.6	18	94.7	0.640
	Alive	2	4.2	1	3.4	1	5.3	
PFS (months)	Median (95%CI)	3.0 (1.7–4.2)		4.0 (1.9–6.0)		0.5–3.4		0.271
OS (months)	Median (95%CI)	5.0 (2.5–7.4)		6.0 (2.0–9.9)		5.0 (1.0–8.9)		0.353

Abbreviations: FOLFİRİNOX, 5-fluorouracil + Leucovorin + Irinotecan + Oxaliplatine; FOLFOX, 5-fluorouracil + Leucovorin + Oxaliplatine; GEMOX, Gemcitabine + Oxaliplatine; PFS, Progression-free Survival; OS, Overall survival.

files. Medical records of 48 patients with mPC treated with capecitabine or gemcitabine in the second-line setting were retrospectively analyzed. Progression-free Survival (PFS) was calculated as the time from the initiation of second-line therapy to the time of progression or death. Overall survival (OS) was calculated as the time from the initiation of the second-line therapy to the time of last follow-up or death. This study was approved by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital (February 26, 2018).

2.3. Statistical analysis

Statistical Package for the Social Sciences for Windows software (Armonk NY, IBM Corp. 2013) was used for the statistical analysis. Numerical variable between two independent groups were analyzed with student t-test in case of normal distribution and with Mann Whitney *U* test if else. The comparison of the rates between the groups was performed by chi-square analysis. Survival was analyzed with Kaplan-Meier method. Determinant factors were examined with cox regression analysis. An overall 5% Type-I error level was used to infer statistical significance.

3. Results

3.1. Patient characteristic

The study included 48 mPC patients, consisting of 26 (54.2%) males and 22 (45.8%) females. The median age of the patients was 62 years (range, 31–82 years). Of the 48 patients, 12 (25%) had diabetes mellitus and 10 (20.8%) had hypertension. The most common sites of metastasis at diagnosis in decreasing order were as follows; liver (95.8%), peritoneum (20.8%), lung (6.3%), distant lymph nodes (4.2%), bone (4.2%), and brain (2.1%). At a median follow-up time of 11.0 months (range, 4.0–39.0 months), 46 (95.8%) patients died (Table-1).

3.2. First-line treatment

The chemotherapy regimens given in the first-line setting were as follows; gemcitabine + cisplatin in 24 (50%) patients, gemcitabine + nab-paclitaxel in 4 (8.3%) patients, FOLFIRINOX in 8 (16.7%) patients, FOLFOX (5-fluorouracil + Leucovorin + Oxaliplatine) in 8 (16.7%) patients, and GEMOX (Gemcitabine + Oxaliplatine) in 4 (8.3%) patients (Table-1).

3.3. Second-line treatment

Twenty-nine (60.5) patients received capecitabine, while 19 (39.5%) patients received gemcitabine in the second-line setting. Patients receiving gemcitabine monotherapy in the second-line setting had received more 5-Fluorouracil-based therapy in the first-line setting, whereas those receiving single-agent capecitabine in the second-line had received more gemcitabine-based treatment, showing a statistically significant difference ($p < 0.001$). Median number of treatment cycles was 4.1 (±2). The rates of partial response, stable disease, and progression at the first response evaluation were 18.8%, 20.8%, and 60.4%, respectively. Grade 3–4 side effects were observed in 10 (20.8%) patients, with 4 (8.3%) of them experiencing hand-foot syndrome, 4 (8.3%) experiencing thrombocytopenia, and 2 (4.2%) experiencing anemia. There was a statistically significant difference in side effect profile between the treatment arms ($p = 0.013$); thrombocytopenia was more frequent in the gemcitabine arm, whereas hand-foot syndrome was more common in the capecitabine arm (Table-1).

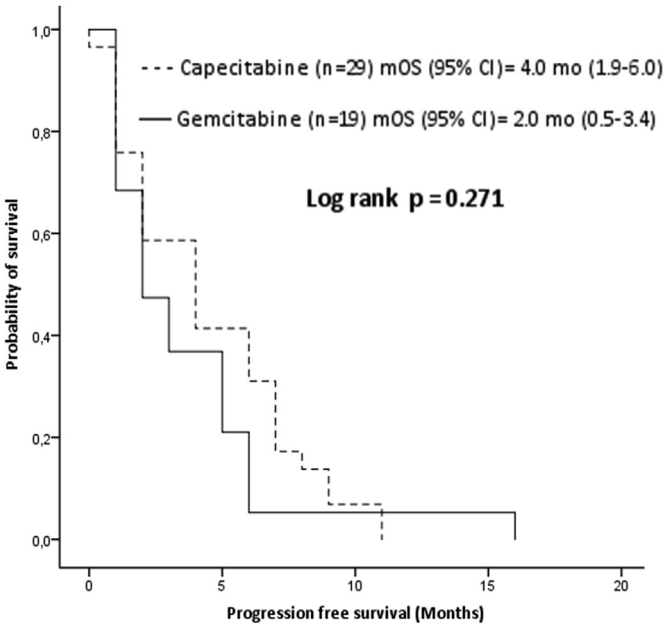

Fig. 1. PFS for treatment groups in second-line.

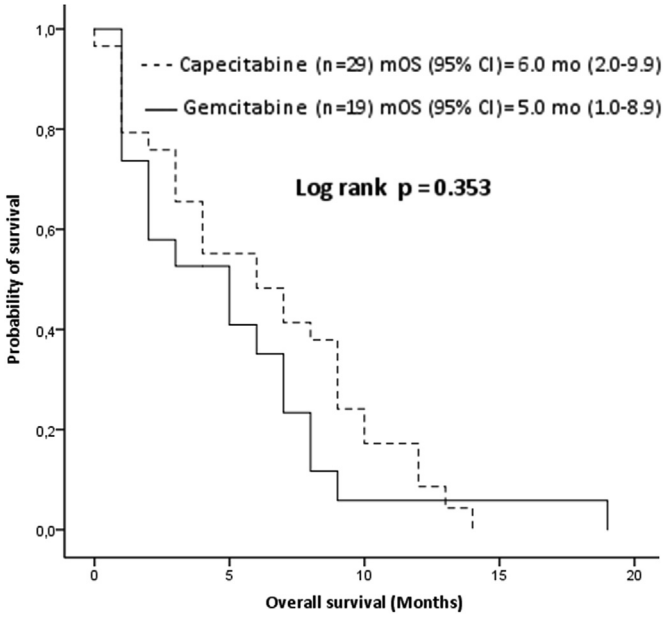

Fig. 2. OS for treatment groups in second-line.

3.4. Third-Line Treatment

After progression on second-line treatment, 3 (10.3%) patients in the capecitabine arm and 1 (5.3%) patient in the gemcitabine arm were able to receive chemotherapy in the third-line setting (Table-1).

3.5. Survival analysis

Median PFS (95% CI) and OS (95% CI) were found to be 3.0 months (1.7–4.2 months) and 5.0 months (2.5–7.4 months), respectively (Table-1). Median PFS (95% CI) was 4.0 months (range, 1.9–6.0 months) in patients receiving capecitabine, whereas it was 2.0 months (range, 0.5–3.4 months) in those treated with

Table 2
Univariate analysis for OS.

		HR	95% CI for HR		p
Age	years	0.987	0.964	1.010	0.278
Gender	male vs. female	0.624	0.341	1.144	0.127
Smoking status	yes vs. no	1.367	0.746	2.505	0.312
Diabetes mellitus	yes vs. no	0.960	0.480	1.921	0.908
Hypertension	yes vs. no	0.784	0.372	1.655	0.523
Liver metastasis	yes vs. no	3.959	0.538	29.117	0.176
Peritoneum metastasis	yes vs. no	1.109	0.529	2.326	0.785
Lung metastasis	yes vs. no	0.696	0.168	2.890	0.618
Distant LN metastasis	yes vs. no	2.120	0.498	9.034	0.309
Bone metastasis	yes vs. no	0.817	0.110	6.058	0.843
Brain metastasis	yes vs. no	1.572	0.212	11.667	0.658
First-line therapy	Cisplatin + gemcitabine	1			0.368
	Gemcitabine+ nab-paclitaxel	1.194	0.354	4.024	0.775
	FOLFIRINOX	1.521	0.640	3.619	0.343
	FOLFOX	2.305	0.999	5.316	0.050
	GEMOX	1.631	0.554	4.797	0.374
Second-line therapy	gemcitabine vs. capecitabine	1.340	0.723	2.482	0.353
Number of cycles in 2nd line		0.728	0.608	0.871	**0.001**
Third-line therapy	yes vs. no	0.402	0.139	1.165	0.093

Abbreviations: See table-1.

gemcitabine (Log rank p = 0.271) (Figure-1). Median OS (95% CI) was 6.0 months (2.0–9.9 months) for patients receiving capecitabine and 5.0 months (1.0–8.9 months) for those treated with gemcitabine (Log rank p = 0.353) (Figure-2). In univariate analysis, the number of cycles given in second-line setting was found to be the factor affecting survival (p = 0.001) (Table-2).

4. Discussion

In this study, the efficacy and tolerability of single-agent gemcitabine was compared to capecitabine in the second-line setting for mPC patients with poor performance status who were not eligible to receive combination chemotherapy regimen and we found that both agents had similar efficacy and tolerability.

Despite many drugs that improve the treatment outcomes of other gastrointestinal system malignancies, to date, improvements in the treatment of pancreatic cancer have remained limited compared to previous decades.[7] Studies have shown that combination therapy is superior to single agent gemcitabine.[4,5,8–10] In the first-line treatment, PFS and response rate were shown to increase with gemcitabine + capecitabine combination compared to gemcitabine alone in the phase 3 clinical trial. In addition, a meta-analysis of two studies comparing the same agents showed a significant improvement in median OS.[7,8] In the PRODIGE study, the FOLFIRINOX regimen vs. gemcitabine alone was shown to significantly prolong median OS in the first-line treatment for mPC patients (median OS 11.1 months vs. 6.8 months, respectively). Moreover, PFS was found to be superior to gemcitabine with FOLFIRINOX regimen.[4] After this study, FOLFIRINOX has become one of the most commonly used regimens in patients with good performance status. Similarly, in MPACT study, median OS with nab-paclitaxel + gemcitabine combination was found to be 8.5 months vs. 6.7 months with gemcitabine monotherapy.[5] The second-line therapy in pancreatic cancer was shown superior to BSC in a phase 3 CONKO study which randomized patients to receive either OFF (oxaliplatine + leucovorin + 5-FU) or BSC. In that study, median OS in the OFF arm was found 4.8 months compared to 2.3 months in the BSC arm.[9] The CONKO-003 study later demonstrated a better OS with OFF regimen than that with FuFA (leucovorin + 5-FU) in patients progressing on first-line gemcitabine monotherapy (median OS 5.3 months and 3.3 months, respectively).[10] However, in the PANCREOX study which was performed in 2016, the superiority of 5-FU + leucovorin-containing regimen (mFOLFOX6) to FuFA could not be demonstrated in terms of PFS and OS.[11] In a phase 2 study performed by Chung et al., median PFS and OS with FOLFIRINOX regimen in mPC patients who progressed on gemcitabine-based treatment were found to be 5.8 months and 9.0 months, respectively.[12] Recently, Girardi et al., demonstrated a PFS of 1.7 months and OS of 6.8 months with a second-line gemcitabine monotherapy in 54 patients who progressed on first-line FOLFIRINOX regimen (pre-treatment ECOG-PS 0 to 1).[13] In one study by De Jesus et al. who included 42 mPC patients with ECOG-PS 0–2, median PFS and OS in patients treated with gemcitabine-based treatment were shown to be 2.9 months and 5.5 months, respectively (64.3% single-agent gemcitabine).[14] In our study, 8 (42%) and 6 (31.6%) patients, who received gemcitabine monotherapy in the second-line setting, had received a first-line FOLFIRINOX and FOLFOX combination, respectively. In addition, 5 patients, who had been treated with a first-line gemcitabine-based therapy, achieved a PFS duration greater than 6 months, hence these patients could receive gemcitabine therapy again. The most common side effect with gemcitabine therapy was thrombocytopenia, with a rate of 21.1%. Treatment was discontinued in 2 patients due to grade 3–4 side effects and disease progression was the main reason for treatment discontinuation in other patients. Median PFS and OS were 2 months and 5 months, respectively.

Bayoglu et al. reported median PFS and OS as 12 weeks and 23 weeks, respectively, with a second-line capecitabine + oxaliplatine regimen in mPC patients with ECOG-PS 0–2 who progressed on first-line gemcitabine-based combination therapy.[15] Similarly, Chung et al. found median PFS and OS as 88 days and 158 days, respectively, in patients receiving capecitabine + gemcitabine regimen after a failure of first-line gemcitabine-based therapy.[16] Bodoky et al. conducted a phase 2 study comparing capecitabine vs. capecitabine + selumetinib combination, demonstrating an OS of 5 months in the capecitabine arm.[17] In our study, 20 (69%) and 4

(13.8%) patients, who received capecitabine in the second-line setting, had received a first-line cisplatin+gemcitabine and gemcitabine+nab-paclitaxel combination, respectively. Additionally, 2 patients received 5-FU-based therapy, one of whom did not want parenteral treatment and received capecitabine, and the other patient was administered capecitabine because of achieving a PFS >6 months. The most common side effect was hand-foot syndrome (13.81%). One patient discontinued the treatment due to grade 3-4 adverse event, whereas disease progression was the main reason for treatment discontinuation in other patients. Second-line therapy with capecitabine provided PFS of 4.0 months and OS of 6 months.

The majority of clinical trials consist of patients with good or excellent performance status (ECOG-PS 0 or 1).[5,8,10,12–17] In the real-world setting, after a failure of first-line therapy, a good performance status (ECOG-PS 0 or 1) is rarely encountered; hence, the patient population included in clinical trials for second-line therapy may not reflect the real-life data. Therefore, there is still no optimal guideline for treatment in patients with ECOG-PS $\geq$2. Although our study included only mPC with ECOG-PS 2, its design was retrospective, with a relatively low number of patients. In addition, the treatment regimens used in the first-line setting were not homogeneous; thus, we do not know how this situation affects the treatment outcomes of next series.

In conclusion, the optimal second-line treatment for pancreatic cancer has not yet been established. In our study, we compared oral capecitabine to gemcitabine in the second-line setting and found that oral capecitabine, which does not require any invasive procedure, had similar outcomes to single-agent gemcitabine in mPC patients who were not eligible for combination chemotherapy regimen. However, prospective, randomized clinical trials including large number of patients are needed to confirm these findings.

Author contributions

Concept – AS, SC; Design – AS, MMA, SS; Supervision – SC, AS, SS; Resources – NY, CG, SS; Materials – AS, NY, CD, MMA; Data Collection and/or Processing – AS, NY, CG; Analysis and/or Interpretation – SC, AS, SS; Literature Search – CD, CG, SS, MMA; Writing Manuscript – AS, SS; Critical Review – SC, CD, SS; Other – MMA, CG, NY.

Conflict-of-interest

All authors declare that there is no conflict of interest related to this article.

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