JBUON 2018; 23 (Suppl 1): S116-S121
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Comparison of gemcitabine monotherapy with gemcitabine and cisplatin combination in metastatic pancreatic cancer: a retrospective analysis

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Summary

Purpose: *Gemcitabine is among the standard first-line agents for the treatment of metastatic pancreatic cancer. However, as the median survival with gemcitabine monotherapy is 6 months, different combinations are being studied for better, prolonged survival. In this multicenter study, we aimed to compare the results of gemcitabine monotherapy with those of gemcitabine and cisplatin combination therapy as first-line treatments for metastatic pancreatic cancer.*

Methods: *Data of 664 patients diagnosed with metastatic pancreatic cancer between January 2007 and December 2016 from seven oncology centers in Turkey were retrospectively evaluated, and 319 patients with gemcitabine alone (n=138) or gemcitabine and cisplatin combination (n=181) as first-line treatment were included.*

Results: *The median patient age was 62 years (range 42-79), being 60 years (42-75) in the gemcitabine/cisplatin arm and 67 years (52-79) in gemcitabine alone arm. no complete response was observed in either arm, whereas partial response rates were 30.1% in gemcitabine/cisplatin arm and 15.3% in gemcitabine alone arm (p=0.001). median overall survival was 8 months (95% CI:7.7–10.2) and was significantly longer in the gemcitabine/cisplatin arm than in the gemcitabine alone arm (10 vs. 6 months, p=0.004).*

Conclusion: *The cemcitabine and cisplatin combination therapy as first-line treatment of metastatic pancreatic cancer yields significantly prolonged survival over gemcitabine monotherapy. In patients with favorable performance conditions, the combination therapy should be preferred.*

Key words: *first-line therapy, gemcitabine plus cisplatin, metastatic pancreatic cancer*

Introduction

Pancreatic cancer is the 13th most common cancer type globally and the 7th cause of cancer-related deaths [1]. Approximately 338,000 new cases were identified in 2012. According to American Cancer Society (ACS), it is expected to be the 3rd cause of cancer-related deaths in 2018 [2]. Most cases with pancreatic cancer present at locally advanced or metastatic stage [3]. In metastatic pancreatic cancer, the prognosis is poor and the 5-year overall survival rate is approximately 1-2%.

Pancreatic cancer is refractory to systemic chemotherapy. Modest efficacy of gemcitabine in

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Received: 14/05/2018; Accepted: 19/06/2018

advanced stages of pancreatic cancer was demonstrated in 1997 [4] and thus, it has been considered the standard treatment of metastatic pancreatic cancer. Considering that the median overall survival with gemcitabine monotherapy is modest (5-7 months) [5], the search for other gemcitabine-based treatments and different combination regimens has increased.

Gemcitabine enters with a single nucleotide increase in the DNA chain, inhibing DNA synthesis and leading to apoptosis. Conversely, cisplatin forms cross-links in DNA, thus inhibiting DNA repair. Owing to these pharmacodynamics [6,7], the first randomized, phase 3 study of gemcitabine and cisplatin combination therapy in metastatic pancreatic cancer was carried out in 2002. In the Colucci et al. study [8] patients with locally advanced or metastatic pancreatic cancer were divided into gemcitabine monotherapy vs. gemcitabine plus cisplatin combination therapy study arms. Objective response rate and time to progression was significantly better in the combination arm. Overall survival was also better in the combination therapy arm, albeit not significantly. The authors mentioned that the statistically significant difference could have been due to the low number of patients and low rates of completion of the six-month treatment, even in patients showing a good response.

There are many past studies on metastatic pancreatic cancer and the treatment regimens currently considered as the standard first-line treatments are as follows; Gemcitabine monotherapy [9,10], FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) [9-11], gemcitabine plus albumin-bound paclitaxel [9,10,12], and gemcitabine plus cisplatin, which is specifically used for hereditary pancreatic cancer patients with DNA repair mutation [9,13].

The aim of the present multicenter study was to compare and evaluate the results of gemcitabine monotherapy vs. gemcitabine and cisplatin combination therapy as first-line treatment in chemo-naive patients with metastatic pancreatic cancer.

Methods

Patients

We retrospectively reviewed the data of 664 patients, who were diagnosed with metastatic pancreatic cancer in seven Oncology centers in Turkey between January 2007 and December 2016 and included 319 patients who received gemcitabine monotherapy or gemcitabine and cisplatin combination therapy as first-line treatment. Of these patients, 25 underwent surgical intervention. Some of the patients undergoing operation were identified as having metastatic cancer intraoperatively, whereas the remaining were detected during postoperative staging imaging procedures (probably due to inadequate baseline staging).

Inclusion criteria were as follows: age ≥18 years, histologically confirmed pancreatic adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2, metastatic disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), and not having previously received adjuvant or palliative chemotherapy or radiotherapy.

Age, sex, ECOG performance status, tumor location, whether or not the patient underwent operation, liver metastasis status, peritoneal metastasis status, the number of metastatic regions, the number of chemotherapy cycles, the causes of chemotherapy discontinuation, and the serum levels of albumin, serum carcinoembryonic antigen (CEA), and serum carbohydrate antigen19-9 (CA-19-9) were determined from patient records and files. Toxicity analysis could not be performed as data regarding toxicity was insufficient.

Factors evaluated in univariate and multivariate analysis

Based on previous studies, 11 variables that might influence overall survival were chosen. Each variable was separated into two subcategories: age (<65 or ≥65 years), sex (male or female), ECOG performance status (0–1 or 2), tumor location (head or body–tail), CEA level (<10 or ≥10 ng/mL), CA 19-9 level (<37 or ≥37 U/mL), albumin (<3.5 or ≥ 3.5 g/dL), liver metastasis (present or absent), peritoneal metastasis (present or absent), biliary stent (present or absent), the number of metastatic regions (1 or ≥2), and the treatment arm (gemcitabine or gemcitabine/cisplatin).

Treatment and Assessment

In the gemcitabine monotherapy arm, gemcitabine was administered on days 1 and 8 at 1200 mg/m^2 of each 21-day cycle, whereas in the combination arm, cisplatin was added at 75 mg/m^2 on day 1 every 21-day cycle to the gemcitabine schedule. All patients received gemcitabine as a 30-min infusion. Gemcitabine plus cisplatin were administered on an outpatient basis as a 2-h infusion (1 liter of 0.9% saline including cisplatin, 20 mmol of potassium chloride, and 8 mmol of magnesium sulfate over 1 hr followed by 500 mL of 0.9% saline over 30 min before the administration of gemcitabine).

Tumor response was evaluated with CT or MR imaging according to the RECIST criteria.

Statistics

Time from the date of diagnosis of tumor metatasis to death was considered as the overall survival. SPSS v18.0 was used for statistical analyses of the data obtained in the study and $p<0.05$ was considered statistically significant. Differences in the characteristics of the two groups were analyzed using Pearson x^2 test. Survival analysis was performed by the Kaplan-Meier method using the log-rank test for comparison between groups. Survival duration was determined in 95% CI (confidence interval). For multivariate analysis, Cox regression test was used.

Results

Patient characteristics

Overall, 319 patients were included in the study, including 138 patients (M:85, F:53) in the gemcitabine (Gem) arm, and 181 patients (M:130, F:51) in the gemcitabine plus cisplatin (GemCis) arm. The patient median age was 62 years (range 42-79), and in the GemCis and the Gem arms it was 60 and 67 years, respectively (p=0.01). Patient characteristics are demonstrated in Table 1. There was no significant difference between the study arms in terms of tumor location (head, neck or tail), previous surgical intervention, the presence of liver metastasis, the number of metastatic regions (1, 2, and ≥ 3), and biliary stents (present or absent).

There was a significant difference between the study arms in terms of the ECOG performance status and the number of treatment cycles. In the Gem arm, 63% and 37% patients had ECOG performance score of 0–1 and 2, respectively, whereas in the GemCis arm, the respective rates were 74% and 26% (p=0.002). In the Gem and GemCis arms,

Table 1. Baseline patient characteristics

Patient characteristics	*Gemcitabine (n=138)*	*Gemcitabine + Cisplatin (n=181)*	*p value*	*Overall (n=319)*
	n (%)	*n (%)*		*n (%)*
Age, years			0.01	
Median	67	60		62
Range	52-79	42-75		42-79
Sex			>0.05	
Female	53 (38.4)	51 (28.1)		104 (32.6)
Male	85 (61.6)	130 (71.9)		215 (67.4)
ECOG			0.02	
0	7 (5)	25 (13.8)		32 (10.1)
1	80 (58)	109 (60.2)		189 (59.4)
2	51 (37)	47 (26)		98 (30.5)
Primary tumor site			>0.05	
Head	74 (53.6)	114 (63)		188 (58.8)
Body	37 (26.8)	44 (24.1)		81 (25.4)
Tail	27 (19.6)	23 (12.9)		50 (15.8)
Previous surgery			>0.05	
R0	12 (8.7)	12 (6.6)		24 (7.5)
R1	7 (5)	5 (2.7)		12 (3.6)
R2	6 (4.3)	3 (1.6)		9 (2.8)
Liver metastasis			>0.05	
Yes	81 (58.7)	122 (67.4)		203 (63.6)
No	57 (41.3)	59 (32.6)		116 (36.4)
Number of metastatic sites			>0.05	
1	95 (68.8)	129 (71.2)		224 (70)
2	30 (21.7)	35 (19.3)		65 (20.4)
≥3	13 (9.5)	17 (9.5)		30 (9.6)
Biliary stent			>0.05	
Yes	47 (34)	38 (21)		85 (26.7)
No	91 (66)	143 (79)		234 (73.3)
Number of cycles			0.006	
1-3	99 (71.7)	108 (59.6)		207 (64.9)
4-6	39 (28.3)	73 (40.4)		112 (35.1)
Reason for stopping chemotherapy			>0.05	
Death	21 (15.2)	11 (6)		32 (9.9)
Progression	44 (31.8)	50 (27.6)		94 (29.4)
Toxicity	15 (10.8)	13 (7.2)		28 (8.7)
Maximal response	15 (10.8)	36 (19.9)		51 (16)
Other	43 (33)	71 (39.3)		114 (36)

Table 2. Tumor response

	Gemcitabine (n=138) n (%)	*Gemcitabine + Cisplatin (n=181) n (%)*	*p value*
Enrolled patients	138 (100)	181 (100)	
Assessable patients	78 (56.5)	136 (75.1)	-
CR	0 (0)	0 (0)	
PR	12 (15.3)	41 (30.1)	0.001
SD	29 (37.2)	61 (44.9)	0.200
PD	37 (47.5)	34 (25.0)	0.001
ORR, %	15.3	30.1	0.001
DCR (CR+RR+SD), %	52.3	75	0.001

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate, DCR: disease control rate

Table 3. Univariate analysis of overall survival by categorical variables

Variables	*Log-rank*	*p value*
ECOG performance status	8.3	0.01
Tumor localization	1.7	0.18
Albumin	15.8	<0.001
Sex	1.5	0.21
CEA	5.9	0.01
CA 19-9	3.1	0.07
Liver metastasis	12.3	0.002
Peritoneal metastasis	0.38	0.82
Age	9.4	0.002
Biliary stent	1	0.60
Number of metastatic sites	2.6	0.26

Table 4. Multivariate analysis of potential prognostic factors associated with overall survival

Factors	*HR*	*95% CI*	*p value*
Treatment arm	0.70	0.50-0.98	0.04
ECOG performance status	1.06	0.83-1.35	0.60
Albumin	0.67	0.49-0.91	0.01
Age	1.04	0.73-1.48	0.79
Liver metastasis	0.64	0.47-0.86	0.004
CEA	1.16	0.84-1.61	0.34
CA 19-9	1.05	0.74-1.49	0.78

HR: hazard ratio, 95% CI: 95% confidence interval

the rates of patients with 4–6 chemotherapy cycles were 28.3% and 40.4%, respectively (p=0.006).

Efficacy

Radiological response evaluation records were available in 78 and 136 patients in the Gem and GemCis arms, respectively. No complete response was observed in either arm, and partial response was observed in 15.3% and 30.1% of patients in the Gem and GemCis arms, respectively (p=0.001) (Table 2). The median overall survival was 8 months

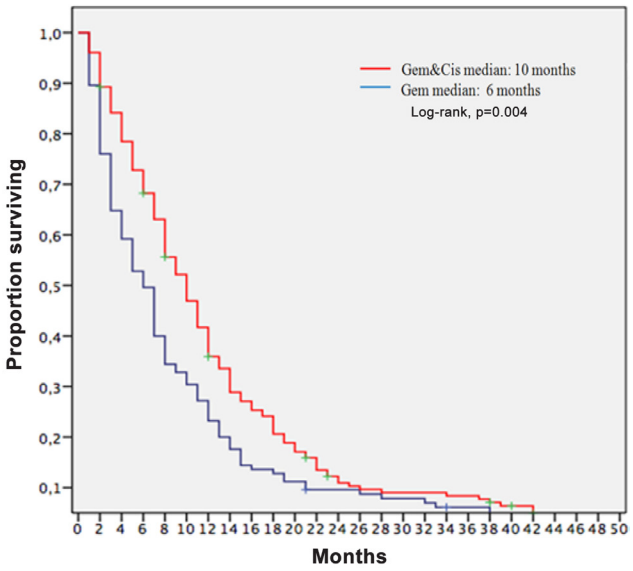

Figure 1. Kaplan-Meier overall survival (Gem:Gemcitabine, GemCis:Gemcitabine plus cisplatin).

(95% CI: 7.7–10.2) and was significantly longer in the GemCis arm compared to Gem arm (6 vs. 10 months, p=0.004) (Figure 1).

Prognostic factors

Of the 11 factors that may have had an effect on overall survival and were evaluated with univariate analysis, 5 were found to have prognostic significance: ECOG performance status (p=0.01), albumin level (<0.001), CEA level (p=0.01), liver metastasis (p=0.002), and age (p=0.002) (Table 3). Seven factors, that were found to be significant or near significant in univariate analysis were submitted to multivariate analysis showing that combination therapy decreased the risk of death by 30% compared to monotherapy (HR:0.70; 95 % CI: 0.50-0.98; p=0.04). Low albumin levels (p=0.01) and liver metastasis (p=0.004) were established as independent unfavorable prognostic factors associated with short survival (Table 4).

Discussion

Metastatic pancreatic cancer is associated with poor prognosis and short survival. It is frequently diagnosed at advanced stages due to its aggressive course and late emergence of symptoms [14]. At this stage, the main aim of treatment is to provide palliative care and possibly improvement of survival. Gemcitabine is one of the main agents used in the treatment of metastatic pancreatic cancer. However, since median survival with gemcitabine monotherapy is only 5-7 months, more effective chemotherapeutic agents are urgently warranted. As literature data show discrepancy on the benefit of adding cisplatin to gemcitabine [8,15-20], we investigated the efficacy of the addition of cisplatin to gemcitabine on overall survival in this retrospective study.

Studies exploring combination therapies on advanced-stage pancreatic cancer have reported that the addition of cisplatin to gemcitabine increases the response rate. In the study of Colucci et al. [8] ORR was 26.4% in the GemCis arm, whereas in the study of Heinemann et al. [15] and the retrospective analysis of Inal et al. [16] ORR was 11.5% and 33.7%, respectively. In the meta-analysis published by Ouyang et al. in 2016 [21], GemCis combination was reported to increase ORR by 48.2% compared to Gem monotherapy, with a significant difference (RR:1.48, 95% CI:1.15-1.91, p=0.003). In the present study, consistent with the literature, ORR was significantly higher in the GemCis arm than in the Gem arm (30.1% vs. 15.3%, p= 0.001).

In most previous studies, it was established that the addition of cisplatin to gemcitabine prolonged the overall survival, yet without significant difference [22]. In the study of Colucci et al. [8], the median overall survival in the GemCis and Gem arms was 7.5 and 5 months, respectively, and in the study of Heinemann et al. [15], it was 7.5 and 6 months, respectively. In the retrospective analysis of Inal et al. [16] and the study of Wang et al. [23], these figures were 12 and 10.2 months, and 9.1 and 7.2 months, respectively.

According to the recent European Society of Medical Oncology (ESMO) and NCCN National Comprehensive Cancer Network (NCCN) guidelines, FOLFIRINOX has been recommended as first-line treatment of metastatic pancreatic cancer with median survival 11.1 months in the FOLFIRINOX arm vs. 6.8 months in gemcitabine monotherapy arm (p<0.001) [11]. In a study using gemcitabine plus nab-paclitaxel, the median overall survival was 8.5 months in the combination arm vs. 6.7 months in the gemcitabine monotherapy (p<0.001) arm [12]. In both phase 3 studies, it was demonstrated that more intensive treatment yielded better results in metastatic pancreatic cancer. In the present study, the combination therapy prolonged survival by 4 months (10 vs 6 months, p=0.004).

Numerous studies have been performed on prognostic factors in pancreatic cancer, and various prognostic factors have been identified in these studies [24-28]. Accurate detection of prognostic factors may also guide the treatment protocol to be utilized. In the studies of Heinemann et al. [15] and Colucci et al. [18], the ECOG performance status was proved independent prognostic factor. In the study of Yi et al. [25], serum C-Reactive Protein (CRP), and albumin levels and liver metastasis were found to be prognostic factors. In the present study, low albumin level (HR:0.67; 95 % CI: 0.4-0.91, p=0.01) and liver metastasis (HR:0.67; 95 % CI: 0.51-0.9, p=0.007) were determined to be negative prognostic factors associated with short survival.

The most important limitation of the present study is its retrospective design and that toxicity data could not be analyzed. Its important advantages are being a multicenter study, having a low probability of bias, and being based on real-life data.

In conclusion, in the literature, there are varying reports on gemcitabine and cisplatin combination therapy in metastatic pancreatic cancer and there is no compelling evidence for the recommendation of this combination therapy as first-line treatment. However, in view of present data, the most commonly accepted general approach is the necessity of using more intensive treatment regimens as first-line treatments of metastatic pancreatic cancer. Among the available treatment regimens, FOLFIRINOX is currently one of the highly recommended treatment regimens. However, its most important problem is high toxicity rates. As pancreatic cancer is a disease of advanced age, tolerance of treatment by this aged patient group is a difficult challenge. Gemcitabine/nab-paclitaxel combination is another treatment regimen which is recommended. However, its high cost limits its use in underdeveloped and developing countries. Based on the data obtained in the present study, it may be suggested that in the first-line treatment of patients with metastatic pancreatic cancer having a satisfactory performance status, gemcitabine and cisplatin combination may be an alternative treatment option.

Conflict of interests

The authors declare no conflict of interests.

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