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Research Article

Can Platinum Plus Gemcitabine be an Alternative to Folfirinox?

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Abstract

Objectives: In cases where homologous recombination repair (HRR) gene analysis is performed, platinum-based chemotherapy is better than other chemotherapy regimens. FOLFIRINOX is the regimen of choice for first-line treatment of pancreatic cancer. However, it is a toxic regimen, and not all patients can tolerate this treatment. Because HRR genes are frequently detected in pancreatic cancer and because FOLFIRINOX treatment cannot be applied to every patient, platinum-based therapies can be used as a first-line therapy. For this reason, we conducted this study to show the first-line effect of a platinum-gemcitabine combination for the treatment of metastatic pancreatic cancer.

Methods: This retrospective and multicenter study included patients admitted to five centers in Turkey between 2010 and 2017. The inclusion criteria were as follows: patients older than 18, diagnosed with metastatic pancreatic cancer, with no previous local treatment (surgery or radiotherapy), with no chemotherapy for metastatic disease, and with an ECOG performance score of 0–2.

Results: A total of 217 patients were included in the study. Of these, 103 were administered gemcitabine alone, and 114 were administered gemcitabine plus cisplatin/carboplatin. Overall survival was significantly longer in the gemcitabine-cisplatin/carboplatin group than in the gemcitabine alone group (9.8 months vs. 5.2 months; p<0.001). Likewise, progression-free survival was statistically significantly longer in the gemcitabine-cisplatin/carboplatin group than in the gemcitabine alone group (4.9 months vs. 3.2 months; p<0.001).

Conclusion: In cases where HRR gene analysis cannot be performed during the treatment of patients with metastatic pancreatic cancer, a patient who cannot tolerate FOLFIRINOX can be treated with a combination of cisplatin/carboplatin-gemcitabine as a first-line treatment. However, larger prospective studies are needed to confirm its effectiveness.

Keywords: Cisplatin, FOLFIRINOX, first line, pancreatic cancer

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Metastatic pancreatic cancer is a highly fatal disease that is generally encountered at an advanced stage due to its late diagnosis.[1, 2] Systemic chemotherapy is usually given to patients in advanced stages, and many studies have been carried out to determine the best choice of chemotherapy. Gemcitabine was first used as a single agent in systemic therapy;[3, 4] however, more effective treatment options have subsequently emerged. The combination of gemcitabine and nab-paclitaxel[5] and treatment with FOLFIRINOX[6] is examples of regimens that prolong overall survival (OS).

Pancreatic cancer susceptibility is increased by the BRCA germline mutation, which is detected in approximately 4–7% of patients with pancreatic cancer.[7–10] The reason is that the BRCA mutation prevents effective DNA damage repair, thereby promoting the development of pancreatic cancer. Nevertheless, damage to the repair mechanism makes the disease susceptible to platinum-based chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors.[11, 12] A phase 2 study conducted in patients with metastatic pancreatic cancer with germline BRCA and PALB2

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mutations investigated the effect of adding veliparib (PARP inhibitor) to the platinum-gemcitabine combination.[13] Compared to platinum-gemcitabine alone, the addition of veliparib did not make a significant contribution to OS or progression-free survival.[13] By contrast, the addition of another PARP inhibitor, olaparib, as a maintenance treatment in patients who responded to chemotherapy extended survival in that group of patients.[14]

The observation that PARP inhibitors can be effective in these cancers suggests that genomic tests in pancreatic cancer (germline mutations) and gene profiling of tumor tissue (such as by next-generation sequencing) should be performed at the time of diagnosis,[15] as this will allow identification of other members of the homologous recombination repair (HRR) group of genes to which BRCA belongs. These other genes include PALB2, ATM, BAP1, BARD1, BLM, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, RAD50, RAD51, RAD51C, and RTEL1. If a somatic or germ line mutation is detected in HRR genes, some changes in treatment may be made. In particular, platinum-based chemotherapy and PARP inhibitors are recommended in this population of patients.[15]

Usually, the choice of chemotherapy is made empirically. FOLFIRINOX is preferred in patients with good performance, but this treatment is toxic and cannot be given to all patients. A gemcitabine nab-paclitaxel combination may be preferred, but it is not a platinum-based treatment and has a higher cost. Platinum-based treatments can be considered as a third alternative, but the previous prospective studies have shown that combination platinum-gemcitabine regimens did not provide statistically significant differences in OS compared to gemcitabine alone.[16, 17] Nevertheless, although no statistical difference was found in survival in these studies, the objective response rates and the progression-free survival were better in the groups given a combination of cisplatin plus gemcitabine.

The aim of the present study was to investigate the effect of platinum-based chemotherapy as a first-line treatment in metastatic pancreatic cancer.

Methods

This retrospective multicenter study included patients admitted to five centers in Turkey between 2010 and 2017. The inclusion criteria were as follows: Patients older than age 18, diagnosed with metastatic pancreatic cancer, with no previously received local treatment (surgery or radiotherapy), with no chemotherapy for metastatic disease, and with an ECOG performance score of 0–2. The patients were divided into two groups according to the treatment that they received. The first group was patients given the combination of carboplatin/cisplatin plus gemcitabine (gemcitabine–cisplatin/carboplatin group); the second group received gemcitabine alone (gemcitabine alone group).

The OS and progression-free survival (PFS) survival results were evaluated. The OS was calculated as the time from the day of the start of chemotherapy to the date of death or the date of the last visit. The PFS was calculated as the time from the start of chemotherapy to the date of progression, death, or the last visit.

The analyzed variables were age (<65 or ≥65 years), gender, ECOG performance score (0–1 vs. 2), tumor localization (head vs. body-tail-end), and metastatic sites (liver, lung). Our study followed the tenets of the Declaration of Helsinki and was approved by the Local Ethics Committee (Manisa Celal Bayar University March 22, 2021-142).

All analyses were performed using the SPSS statistical software program package (SPSS version 20.0 for Windows). The differences in the clinical characteristics between the two groups were analyzed by a Chi-square test. The OS and PFS were calculated with the log-rank test. The Kaplan–Meier method was used to construct survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS and PFS. Differences were assumed to be significant when p value was <0.05.

Results

A total of 217 patients were included in the study. Of these patients, 103 were administered gemcitabine alone (gemcitabine alone group), while 114 were administered gemcitabine plus cisplatin/carboplatin (gemcitabine-cisplatin/carboplatin group). The characteristics of the patients are shown in Table 1. Multivariate analysis revealed that only the ECOG performance score showed a statistically significant difference in terms of OS (Table 2). The proportion of patients with an ECOG performance score of 2 was significantly higher in the gemcitabine alone group (p<0.001).

The OS was significantly longer in the gemcitabine-cisplatin/carboplatin group than in the gemcitabine alone group (9.8 months vs. 5.2 months p<0.001). Likewise, the PFS was significantly longer in the gemcitabine-cisplatin/carboplatin group than in the gemcitabine alone group (4.9 months vs. 3.2 months; p<0.001). The OS results are shown in Fig. 1, and the PFS results are shown in Fig. 2.

Discussion

In metastatic pancreatic cancer, where life expectancy is short, first-line chemotherapy is the most important factor that determines survival. The FOLFIRINOX regimen has demonstrated the longest OS in randomized studies to

Table 1. General characteristics of patients

	Gemcitabine alone group (n=103)	Gemcitabine-cisplatin/ carboplatin group (n=114)	Overall (n=217)
Age, years			
Median	63.69	59.18	61.32
Range	38–81	31–79	31–81
p=0.002			
Sex			
Female	59	72	131
Male	44	42	86
p=0.228			
ECOG			
0–1	73	104	177
2	30	10	40
p<0.001			
Primary tumor side			
Head	54	63	117
Body-tail	48	55	100
p=0.491			
Overall	103	114	217

*P-value shows whether the distribution of the variable between the two groups is statistically significant.

Table 2. Multivariate analysis

	Significance (p)	Hazard ratio
Age	0.470	0.888
Gender	0.943	0.988
ECOG performance score	0.000	2.502
Tumor localization	0.572	1.094
Liver metastasis	0.702	0.929
Lung metastasis	0.539	0.876

*Variable that effects overall survival. Only ECOG performance status effect overall survival.

date. However, the combination of cisplatin-gemcitabine has shown the longest survival in patients with HRR mutations.[15] In the present study, the combination of cisplatin-gemcitabine provided a survival of approximately 15 months (only patients with BRCA1-2 and PALB2 mutations were included), indicating the success of platinum-based chemotherapy in the patient population with an HRR mutation. Approximately 4–7% of patients with metastatic pancreatic cancer have BRCA mutations, but this number will undoubtedly increase as other HRR genes are studied. Therefore, the findings presented here emphasize the importance of platinum-based drugs as a first-line therapy.

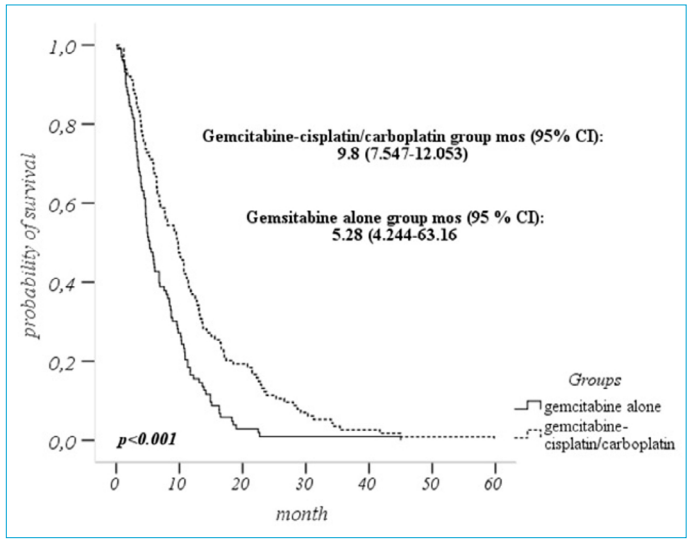

Figure 1. Overall survival of all patients.

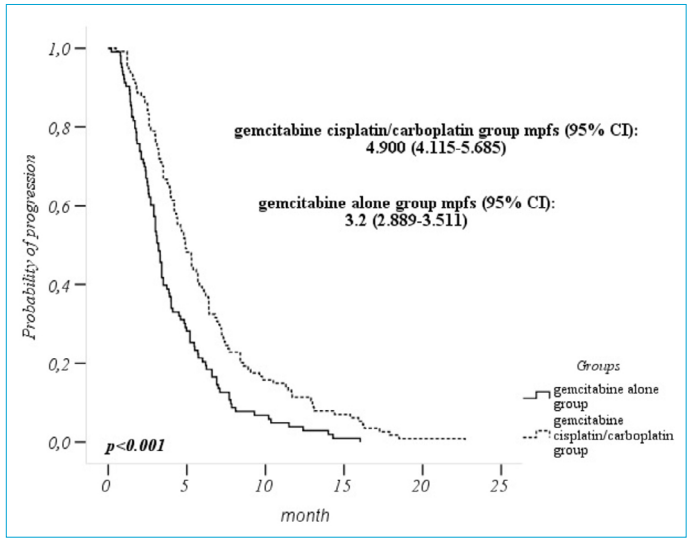

Figure 2. Progression-free survival of all patients.

In our study, the OS and PFS were statistically significantly longer in the patient group given gemcitabine-cisplatin/carboplatin than in the group receiving gemcitabine alone. As this was a retrospective study, the non-homogeneity of the patients between the groups may have contributed to this difference, as the number of patients with low-performance scores (which had the greatest effect on survival) was higher in the gemcitabine arm. However, some patients (approximately 9%) with ECOG performance scores of 2 were also present in the platinum gemcitabine arm. Considering that only patients with ECOG scores of 0–1 were included in the FOLFIRINOX study and that the OS was 11.1 months, the 9.8-month survival in the platinum-gemcitabine arm in our study is an important indicator of the success of these drugs.

Examination of gemcitabine nab-paclitaxel, another com-

bination first-line chemotherapy, showed an OS of 8.5 months in the combination arm. Patients with low-performance scores were also included in that study (Karnofsky; 60–70 patients participated). The patients taking gemcitabine nab-paclitaxel appeared to have a similar performance; however, survival was higher numerically.

In our study, the PFS was statistically significantly longer with the platinum-gemcitabine combination than with gemcitabine alone, in agreement with the findings of all large-scale studies. Comparison of these studies showed that the numerical terms show only very small differences, and the results from all the studies are close to each other.

At present, analysis of HRR genes is recommended in patients with metastatic pancreatic cancer;[15] however, this is not always possible and empiric treatments are performed. Platinum-based therapy is recommended in patients with somatic or germline mutations in HRR genes,[15] and two options stand out as platinum-based treatments. The first is the FOLFIRINOX regimen, which is currently the first option in patients with good performance. The second option is the carboplatin/cisplatin-gemcitabine combination. FOLFIRINOX is a toxic treatment, so it cannot be used for all patients. Therefore, in cases where FOLFIRINOX cannot be used, a combination of cisplatin/carboplatin-gemcitabine may be preferred as the first-line treatment. The OS figures of the gemcitabine–nab-paclitaxel combination, which is the other recommended option when FOLFIRINOX cannot be given, are close to the OS figures of the cisplatin/carboplatin-gemcitabine regimen. However, the gemcitabine–nab-paclitaxel combination is not a platinum-based combination, so its effectiveness in patients with a mutation in the HRR gene is relatively low. Larger prospective studies are needed to resolve this issue.

Conclusion

In cases where HRR gene analysis cannot be performed when treating patients with metastatic pancreatic cancer, if the patient cannot tolerate FOLFIRINOX, a combination of cisplatin/carboplatin-gemcitabine can be used as a first-line treatment. However, larger prospective studies are needed to confirm its effectiveness.

The authors are in agreement with the content of this manuscript. They also declare that they have no conflicts of interest. The study with accompanying material is an original work and neither published, accepted, or submitted for publication elsewhere.

Disclosures

Ethics Committee Approval: Our study followed the tenets of the Declaration of Helsinki and was approved by the Local Ethics Committee (Manisa Celal Bayar University March 22, 2021-142).

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