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Research Article

Options in First Line Management of Metastatic Pancreatic Cancer and the Determinative Role of ECOG Performance Status

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Abstract

Objectives: It will contribute to the fact that the first-line treatment options of patients with metastatic pancreatic cancer (PC) who apply to the oncology clinic are discussed in the light of the literature and guide the clinicians in making the initial treatment decision.

Methods: Patients who were diagnosed with PC in a total of 2 centers between 2010 and 2019 and who were found to have distant organ metastases at the time of diagnosis or during follow-up were included. Patients were categorized into 3 groups in terms of metastatic first line treatments: gemcitabine (Gm), gemcitabine-platinum (cisplatin or carboplatin) (GP) combination and FOLFIRINOX (FX). These three treatment groups were compared in terms of patient with tumor characteristics and progression free survival (PFS) - overall survival (OS).

Results: The present study included 355 patients who were admitted to our clinic. The first line therapies received by the patients were analyzed, it was seen that 124 (34.9%) patients received Gm chemotherapy (CT), 43 (12.1%) patients received FX, 138 (38.9%) patients received GP and 18 (5.1%) patients received other regimens. While PFS was 6.1 months in GP areas, it was the shortest with 4.4 months in Gm and the longest with 7.1 months in FX. This difference between the groups was found to be statistically significant ($p<0.001$). When the data were analyzed in terms of OS; the Gm arm was found to have the shortest OS with 9.6 months. However, GP attracted attention as the treatment that prolonged the OS the most with 15.4 months. This period was calculated as 13.5 months in the FX arm. Again, this difference was found to be statistically significant ($p<0.001$).

Conclusion: The main theme of our study was that 'Eastern Cooperative Oncology Group' performance status (ECOG PS) and age were the most important factors in decision making for the management of these patients. As age progresses and PS deteriorates, clinicians move away from the FX regimen. Another important point was that the GP regimen was preferred instead of GnP, probably due to the difficulty in drug supply in our country, and it was found to be superior to other regimens.

Keywords: ECOG PS, FOLFIRINOX, Gemcitabine-Platinum, Overall Survival, Pancreatic Cancer

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PC has an aggressive course and is mostly diagnosed at advanced stages. Although the only chance of curative treatment is surgery, only a small minority of patients, such as 15-20%, are candidates.[1] Apart from the high probability of distant metastasis, invasion of the surrounding arteries and veins, which requires neoadjuvant therapy, also complicates the operation option.[2] Despite surgery, the disease recurs with local recurrence and distant metastases in the majority of patients. In order to minimize this possibility, adjuvant CT is recommended even at very early stages (T1N0M0) in those who do not receive neoadjuvant therapy.[3]

While the 5-year survival rate remains around 20%[4] even in those who have been operated on, this rate is around 5-8% in patients diagnosed at the inoperable or metastatic stage.[4,5] At this stage, it should be discussed with the patient that the CT is planned for palliative purposes and not for a curative result, and patients should be directed to clinical studies as much as possible.[2,3] Priority should also be given to reducing symptoms related to other diseases, especially pain. One purpose of the planned CT is to assist tumor-related symptom palliation, while the other purpose is to prolong survival.[6] After the initiation of palliative treatment, the patient's PS should be evaluated in terms of compliance with CT regimens.[2,3,6]

In patients presenting with a diagnosis of PC, the first determining factor in the CT decision should be the patient's PS. According to the ECOG criteria (Table 1), the FX regimen, which is a triple treatment modality for the fully active (ECOG 0) and the patient group who experience difficulty in strenuous physical activity (ECOG 1). It is included in the group that should be preferred.[2,3,7] However, as the performance of the patients decreases, it becomes difficult to tolerate this treatment and the possibility of benefiting from the treatment decreases. For patients who are mobile more than 50% of the time they need to stay awake, the treatment strategies are now limited to FOLFOX (fluorouracil and oxaliplatin), Gm and albumin-bound paclitaxel (nab-paclitaxel) in the group whose performance capacity is limited only to personal care ability (ECOG 2) and focuses on dual regimens such as GP.[7] In patients who have to spend most of their time in bed (ECOG 3), the basis of the approach to the patient should be the gentle continuation of the palliative treatment recommended initially. In these patients, the CT decision should only be made on a patient basis and with a very good physician-patient dialogue.[7]

Table 1. ECOG Performance Status Diagnostic Criteria

ECOG 0	Fully active; no performance restrictions.
ECOG 1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
ECOG 2	Capable of self-care but unable to carry out any work activities; up and about >50% of waking hours.
ECOG 3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
ECOG 4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

ECOG: Eastern Cooperative Oncology Group.

While ECOG PS maintains its role as an unchanging factor in making treatment decisions, homologous recombination repair (HRR) gene mutations should be examined immediately in respect of treatment selection, because if these mutations are detected, the treatment should be established based on platinum. At 4 months after the start of treatment, maintenance can be performed with poly (ADP-ribose) polymerase (PARP) inhibitors.[2] However, despite the development of promising treatment options with immunotherapy and other targeted drugs, which are new treatment modalities for cancer treatment, the main treatment strategy of PC is still conventional CT. While deciding on limited treatment agents, many other variables such as the patient's comorbidity status, expected drug toxicity, and laboratory values should also be taken into account.[7,8]

The aim of this study was to contribute to literature through a review of the first-line treatment options of patients with metastatic PC who presented at the oncology clinic and thereby guide clinicians in making the initial treatment decision.

Methods

Study Population

The patients included in this study were those who were diagnosed with PC in a total of 2 centers between 2010 and 2019. Patient records were reviewed retrospectively. The patients who were found to have distant organ metastases at the time of diagnosis or during follow-up. Patients with metastases detected by computed tomography, magnetic resonance imaging or positron emission tomography were included in the study. Patients with synchronous tumors who were not metastatic and whose data could not be reached were excluded from the study.

A record was made of data of age, gender, ECOG PS, primary tumour localization, surgical history, surgical margin status, stage at the time of diagnosis, localization of metastasis, first-line therapy and the number of treatment lines received at metastasis. PFS was recorded as the time from the determination of the first metastasis to the date of the

first detected radiological progression. OS was defined as the time from diagnosis of metastatic disease to death or the last follow-up examination at the time of the end of the study.

Patients were categorized into 3 groups in terms of metastatic first-line treatments: Gm, GP and FX. These three treatment groups were compared in terms of patient and tumor characteristics and PFS - OS.

Statistical Analysis

The data obtained in the study were analysed statistically using IBM SPSS Statistics vn. 18.0 software.

Categorical variables were stated as number (n) and percentage (%), and continuous variables as median. Conformity of the data to normal distribution was assessed. To evaluate relationships between two categorical variables, the Chi-square and Fisher Exact tests were used. Survival analysis was performed using the Kaplan- Meier method and statistical comparisons of potential predictive factors were made using Log-Rank analysis for univariate analysis. A value of $p<0.05$ (two-sided) was accepted as statistically significant.

Results

Patient Characteristics

Evaluation was made of 355 patients who were admitted to our clinics, comprising 64.8% (230) males and 35.2% (125) females with a median age of 57 years (range, 31-88 years). The clinicopathological features of the patients are summarized in Table 2. Pre-treatment ECOG PS of the patients was determined as 0 in 103 (29%) patients, 1 in 190 (53,5%), 2 in 54 (15.2%), 3 in 7 (2%), and 4 in 1 (0.3%). Previously, only 67 (18.9%) patients underwent surgical resection and metastasis developed afterwards. 285 (80.3%) patients were diagnosed in the inoperable or metastatic stage. Lung metastasis was determined in 83 (23.4%) patients and liver metastasis in 246 (69.3%) patients. When examined in terms of primary tumor localization, the most common place was reported as the head of the pancreas in 211 (59.4%) patients.

Treatment

When the first-line therapies received by the patients were analyzed, it was seen that 124 (34.9%) patients received Gm, 43 (12.1%) patients received FX, 138 (38.9%) patients received GP and 18 (5.1%) patients received other regimens. When the number of treatments received in the metastatic line was questioned, it was observed that 176 (49.6%) patients received at least one line of therapy, and 6 (1.7%) patients received 4-line treatment.

Table 2. Demographic and clinical characteristics of the patients

No of patients	355
Median age (range)	57 (31-88)
Male [No. (%)]	230 (64.8)
Female [No. (%)]	125 (35.2)
ECOG PS [No. (%)]	
0	103 (29)
1	190 (53.5)
2	54 (15.2)
3	7 (2)
4	1 (0.3)
Localization of metastasis [No. (%)]	
Lung	83 (23.4)
Liver	246 (69.3)
Stage at the time of diagnosis [No. (%)]	
Stage 1 A	5 (1.4)
Stage 1 B	13 (3.7)
Stage 2 A	1 (0.3)
Stage 2 B	24 (6.8)
Stage 3	35 (9.9)
Stage 4	276 (77.7)
Surgical resection. [No. (%)]	
Yes	67 (18.9)
No	285 (80.3)
Data is insufficient.	3 (0.8)
Surgical magrin status [No. (%)]	
Positive	11 (3.1)
Negative	43 (12.1)
Not evaluated	12 (3.4)
Primary tumor location. [No. (%)]	
Head	211 (59.4)
Body	70 (19.7)
Tail	59 (16.6)
Other	15 (4.2)
First line therapy. [No. (%)]	
Gemcitabine	124 (34.9)
Gemcitabine-platin combined	138 (38.9)
Folfirinox	43 (12.1)
Other	18 (5.1)
Not receiving any treatment.	32 (9)
Number of treatment lines received at metastasis. [No. (%)]	
1	176 (49.6)
2	113 (31.8)
3	27 (7.6)
4	6 (1.7)

ECOG PS: Eastern Cooperative Oncology Group Performance.

Treatment groups were analyzed in terms of patient characteristics. The median age of patients receiving Gm was 63.83 years, 59.20 years in the GP, and 57.51 years in the FX

arm. This difference was found to be statistically significant (p<0.001).

When the treatment groups were evaluated in terms of ECOG PS, it was seen that the GP combination was preferred most in 44 (14.4%) and 82 (26.9%) patients, respectively, in the groups with ECOG PS 0 and 1. The FX regimen was preferred least for 21 patients (6.9%) in each of the ECOG PS 0 and 1 groups. Gm was given to 31 (10.2%) patients with ECOG PS 2, GP was given to 12 (3.9%) patients, and the FX regimen was not preferred in this group. This difference was found to be statistically significant (p< 0.001). Gender, localization of metastasis, stage at the time of diagnosis, surgical resection and surgical margin status were similar between the groups (Table 3).

Survival Analysis

The median OS of the patients was calculated as 10.3 months and all were exitus at the date of data analysis. PFS of patients was calculated as 5.2 months, regardless of the first-line treatment type. While PFS was 6.1 months in GP areas, it was the shortest at 4.4 months in Gm and the longest at 7.1 months in FX. This difference between the groups was found to be statistically significant (p<0.001) (Fig. 1).

When the data were analyzed in terms of OS, the Gm arm was found to have the shortest OS with 9.6 months. GP was observed to be the treatment that prolonged OS the most at 15.4 months. This period was calculated as 13.5 months in the FX arm. This difference was found to be statistically significant (p<0.001) (Table 4, Fig. 2).

Table 3. Clinicopathological features of first line treatment arms

	Gemcitabin	Gemcitabin-platin combined	Folfirinox	p
Median age (min-max)	63.83 (38-81)	59.20 (31-79)	57.51 (44-77)	<0.001
Gender				0.390
Male [No. (%)]	78 (25.6)	91 (29.8)	32 (10.5)	
Female [No. (%)]	46 (15.1)	47 (15.4)	11 (3.6)	
ECOG PS [No. (%)]				
0	22 (7.2)	44 (14.4)	21 (6.9)	<0.001
1	68 (22.3)	82 (26.9)	21 (6.9)	
2	31 (10.2)	12 (3.9)	0 (0)	
3	2 (0.7)	0 (0)	1 (0.3)	
4	1 (0.3)	0 (0)	0 (0)	
Localization of metastasis [No. (%)]				
Lung	32 (10.7)	27 (9)	12 (4)	0.417
Liver	91 (30.3)	93 (31)	28 (9.3)	
Stage at the time of diagnosis [No. (%)]				
Stage 1 A	0	4 (1.1)	0	0.169
Stage 1 B	3 (0.8)	5 (1.4)	2 (0.5)	
Stage 2 A	0	0	1 (0.2)	
Stage 2 B	5 (1.4)	8 (2.2)	4 (1.1)	
Stage 3	11 (3)	15 (4.2)	4 (1.1)	
Stage 4	105 (29.5)	106 (29.8)	32 (9)	
Surgical resection. [No. (%)]				
Yes	17 (5.6)	23 (7.6)	9 (3)	0.551
No	105 (34.7)	115 (38)	34 (11.2)	
Surgical magrin status [No. (%)]				
Positive	6 (10.3)	5 (8.6)	0	0.727
Negative	18 (31)	17 (29.3)	5 (8.6)	
Not evaluated	4 (6.9)	2 (3.4)	1 (1.7)	
Primary tumor location. [No. (%)]				
Head	67 (22)	82 (26.9)	27 (8.9)	0.085
Body	26 (8.5)	33 (10.8)	6 (2)	
Tail	20 (6.6)	19 (6.2)	10 (3.3)	
Other	11 (3.6)	4 (1.3)	0	

ECOG PS: Eastern Cooperative Oncology Group Performance.

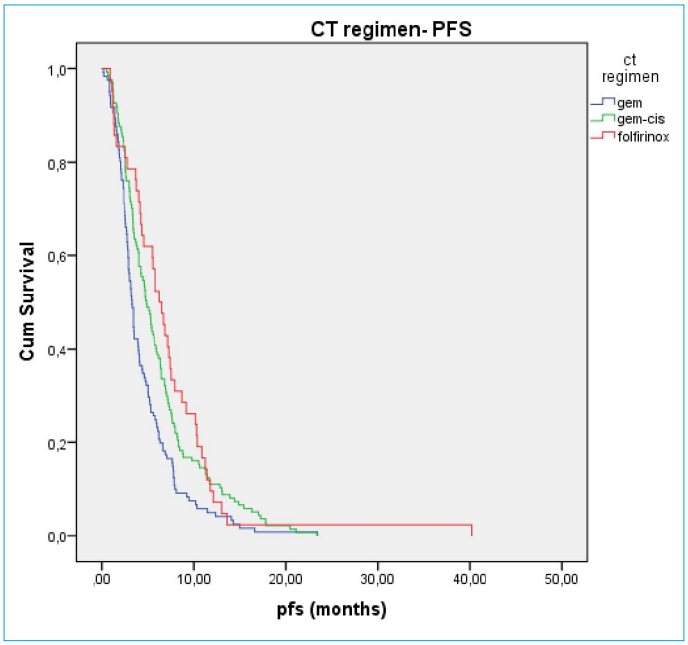

Figure 1. The progression-free survival (PFS) of patients was calculated as 5.2 months, regardless of the first line treatment type. While PFS was 6.1 months in GP areas, it was the shortest with 4.4 months in Gm and the longest with 7.1 months in FX. This difference between the groups was found to be statistically significant (p<0.001).

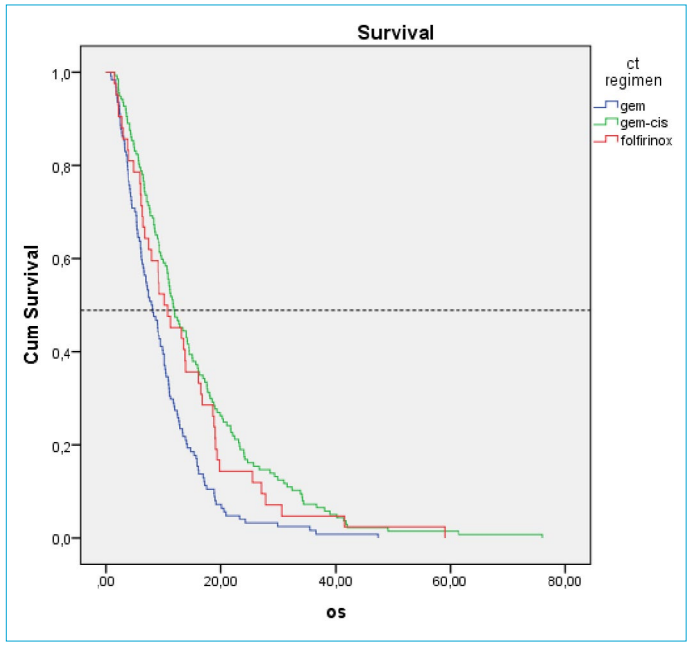

Figure 2. The Gm arm was found to have the shortest OS with 9.6 months. However, GP attracted attention as the treatment that prolonged the OS the most with 15.4 months. This period was calculated as 13.5 months in the FX arm. Again, this difference was found to be statistically significant (p<0.001).

Table 4. Association between study subjects and PFS - OS

Characteristics	Median PFS (95% CI Lower-Upper)	p	Median OS (95% CI Lower-Upper)	p
Gender				
Female	5.6 (4.7-6.5)	0.561	12.8 (10.7-15)	0.701
Male	5.3 (4.7-5.9)		12,3 (10.9-13.8)	
ECOG PS				
0	7.4 (6.1-8.6)	0.001	20 (17.1-22.9)	<0.001
1	5 (4.5-5.6)		10,7 (9.5-11.9)	
2	3.2 (2.4-4.1)		6.2 (4.8-7.6)	
3-4	1.2 (0.5-3)		3.8 (1-6.6)	
Localization of metastasis (Liver)				
Yes	5.1 (4.5-5.8)	0.072	11 (9.7-12.2)	<0.001
No	6.2 (5.2-7.1)		15.6 (13-18.3)	
Localization of metastasis (Lung)				
Yes	5.4 (4.9-6)	0.829	12.4 (9.5-15.3)	0.936
No	5.6 (4.4-6.8)		12.3 (11-13.6)	
Primary tumor location				
Head	5.3 (4.5-6)	0.647	12.8 (11.2-14.4)	0.830
Body	5.3 (4.4-6.2)		11.8 (9.3-14.2)	
Tail	6.2 (4.9-7.5)		12.7 (9.7-15.8)	
Other	5.6 (3.5-7.7)		10.6 (6.3-15)	
First line therapy				
Gemcitabine	4.4 (3.7-5)	0.001	9.6 (8.2-10.9)	<0.001
Gemcitabine-platin	6.1 (5.3-6.8)		15.4 (13.3-17.5)	
FOLFIRINOX	7.1 (5.1-9.1)		13.5 (9.9-17)	

ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRINOX: Fluorouracil-Oxaliplatin-Irinotecan; PFS: Progression-Free Survival; OS: Overall Survival.

Discussion

Performance status is a very important concept for cancer care and treatment, which predicts a patient's ability to perform certain daily life activities without the help of others. It plays a role in both determining the prognosis and determining the best treatment for the patient, because patients with worse PS tend to have lower tolerance of cancer treatments. These patients have less positive results than patients with better PS, regardless of the planned treatment.[9] ECOG PS is the most commonly used scale for PC, and it is basically designed by scoring from 0 to 4. In this scoring, "0" indicates that the patient is fully functional and asymptomatic and "4" indicates the state of being bedridden (Table 4). When the 355 PC patients who were evaluated for first-line treatment in the oncology clinic were evaluated in this perspective, the GP (14.4%) was seen to be the preferred CT regimen, even more than the other two regimens, for 87 patients with ECOG PS 0. FX, on which the international guidelines form a consensus, was the least preferred regimen at a rate of 6.9%.[1-3] The same trend was seen in those with ECOG PS 1. In this group, GP was preferred in 82 of 171 patients, and the treatment least administered was FX. As expected, the triple regimen was not preferred at all in the ECOG PS 2 group, where Gm treatments should be established. The difference between these treatments based on PS was also statistically significant ($p<0.001$). When the patient characteristics of the treatment groups were examined, characteristics other than age showed a similar distribution. As the average age of the patients increased, the preference shifted from the triple regimen to monotherapy. This evaluation based on the average age was also statistically significant ($p<0.001$).

When the treatments given were examined in terms of PFS, it was observed that the FX regimen was the treatment modality applied for the longest time at 7.1 months (95% CI: 5.1-9.1) ($p<0.001$), but similar benefit was not obtained in OS. The treatment that prolonged OS the most was GP ($p<0.001$) at 15.4 months (95% CI: 13.3-17.5). For FX, there was seen to be a survival benefit of 13.5 months (95% CI: 9.9-17). Gm treatment was determined to prolong both PFS and OS by 4.4 months and 9.6 months, respectively, compared to other combination regimens.

Although FX was the least preferred regimen in this study, international treatment guidelines such as The European Society for Medical Oncology (ESMO) guidelines, the National Comprehensive Cancer Network (NCCN) guidelines and the American Society of Clinical Oncology (ASCO) recommend gemcitabine-nab-paclitaxel (GnP) or FX therapy as first line in patients with ECOG PS 0-1.[10,11] Although the survival benefit of these combination regimens compared to those who do not receive treatment is limited to a few months, this difference is meaningful in terms of patient benefit due to the limited treatment options, the lack of an optimal option in the further steps, and patients not being able to receive the treatments to be recommended in other steps.[12,13] However, these recommendations of international guidelines are not reflected in the countries and clinician preferences in the same way. A study in 2020 comparing the first-line treatment regimens of 2565 patients with metastatic PC by 225 different clinicians provides a perspective on this issue.[13] While FX is the most commonly used regime in France and the United Kingdom, Gm/GP regimes take priority in Italy and Spain.[13] The unchanged option for FX was more preferred for those under 65 years and ECOG PS 0-1. Another striking point was that Gm was the second most preferred regimen in France and the UK, but was less preferred in other countries. When examined in terms of survival, FX and PFS are seen to be around 10 months, and OS increases up to 16 months. In the current study, the PFS/OS value provided by FX was reported as 7.1-13.5. Again, for those who prefer GnP and Gm in the primary care, the OS was 12 months and 9 months, respectively. Undoubtedly, reasons such as patient characteristics, clinician experience, and access to medication have a place in the decision making. As there is a shortage of access to drugs for GnP in Turkey, when gemcitabine-based treatment is desired, it is combined with platinum, as in the current study. The study results showed that OS was 15.4 months in the GP combination and 9.6 months for Gm. This suggests that in terms of survival benefit, the GP combination can be given primarily in cases where GnP cannot be given. However, it must be emphasized that HRR gene mutation analyses should be performed in order to select patients who will benefit from platinum treatment.[2,7,8,13]

A study by Nha Le et al, which analyzed real-world clinical practice with FX and GnP in patients diagnosed with PC across Europe, was designed unconventionally and provided interesting results. Through a web-based questionnaire, 5420 physicians, half of whom were medical oncologists, in 19 different countries, were asked about their primary care preferences and reasons. The physicians emphasized that they mostly preferred the GnP regimen to the FX regimen, with 47% stating toxicity as the reason. Of the total physicians 42% preferred to use FX, and 11% preferred to use it in combination with Gm or erlotinib.[14] In addition, 57% of the clinicians stated that more clinical studies with GnP are needed. When we integrate these results with the fact that FX is less preferred than it should be in the current study, it can be concluded that clinicians are looking for an alternative effective treatment regimen with fewer side-effects.[14]

In an original study of 342 patients with ECOG PS 0-1 by Con-

roy et al. in 2011, which compared FX with Gm, allowing it to enter routine practice on PC, the PFS/OS results of FX were found to be superior to Gm at 6.4/11.1 months and 3.3/6.8 months, respectively.[15] However, FX was found to be highly toxic, especially in terms of hematological toxicities, neuropathy, diarrhea and liver function tests. Undoubtedly, it is not enough for a treatment to be effective only, but it must also be tolerable and able to be continued as planned. Therefore, the incompatibility of FX in efficacy and tolerance scales, creates a potential dilemma for clinicians.

One of the studies that changed our routine practice in PC treatment, is the MPACT study of 861 patients in which GnP and Gm were compared. From the point of view of OS, it was seen that GnP (8.7 months) was more effective than Gm (6.6 months) ($p < 0.001$). Although the side-effect profile was slightly higher in the GnP arm, it did not appear to be as toxic as FX.[15,16] However, when it is necessary to prioritize the survival benefit, undoubtedly, the benefit provided with GnP is more in the background compared to FX.[15-17] In a recent study of 37 patients, survival of 14.6 months was obtained by sacrificing irinotecan or oxaliplatine in the combination when necessary to make the FX regimen more tolerable, and it was stated that the regimen can be modified individually. However, the retrospective design of that study and the small number of patients were limitations.[15,18] Modified regimens are not limited to that study, and researchers have been interested in using different formulas for a long time to increase FX tolerance.[17,19]

The combination of GP, which is the less popular treatment regimen in the treatment of metastatic PC today, was superior to the other two regimens in the current study, showing an overall survival benefit of 15.4 months ($p<0.001$). The first randomized controlled clinical study involving 400 patients, designed with the idea of adding platinum to Gm, was published by Colucci et al. in 2010.[20] Similar to the current study, the characteristics and number of patients were homogeneously distributed. The most important difference from the current study was that weekly cisplatin was added to gemcitabine instead of in 21-day cycles. However, unfortunately, as in other similar studies, the combination arm did not show superiority to Gm in terms of either PFS or OS.[21,22] Another interesting point drawn from these studies is that using PS as a basis does not change the results. However, in the light of all these data, if the current study is regarded from a platinum perspective, the prolonged survival provided by GP can be seen to be valuable. With the increase in real-life data, it is hoped that it will be among the options again.

The aim of this study was to evaluate especially the role of ECOG PS and the treatment preferences of clinicians in the complex patient selection and decision-making process for primary care management of metastatic PC patients. At the same time, it was aimed to show the real-life equivalent of original studies that guide clinical practice and are included in the guidelines.

Conclusion

The main outcome of this study was that ECOG PS and age were the most important factors in decision-making for the management of these patients. As age progresses and PS deteriorates, clinicians move away from the FX regimen. Another important point was that the GP regimen was preferred instead of GnP, probably due to the difficulty in drug supply in Turkey.

Disclosures

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Ethics Committee Approval: Ethics committee approval was obtained numbered 'E-85252386-050.04.04-49116'. No humans or animals were used for this research.

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Conflict of Interest: None declared.

Authorship Contributions: Concept – F.E.; Design – F.E.; Supervision – F.E.; Materials – A.P.E.; Data collection &/or processing – S.Y.; Analysis and/or interpretation – A.Ö.; Literature search – A.P.E.; Writing – F.E.; Critical review – A.P.E.

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