ORIGINAL RESEARCH

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The Real-Life Efficacy of the Second Line Treatment Strategy in Advanced Pancreas Cancer

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ABSTRACT Objective: Pancreatic cancer is one of the leading causes of cancer-related death. Despite the introduction of new therapeutic agents, survival rates remain low. Furthermore, few trials have evaluated the options for second-line therapy and the prognostic variables. In this study, we aimed to determine the real-world efficacy and prognostic parameters of second-line treatment for advanced pancreatic cancer. **Material and Methods:** Patients with advanced pancreatic cancer from different centers who received second-line treatment were enrolled in the study. The patients' demographic, clinical, and pathological characteristics were retrieved retrospectively. **Results:** A total of 161 patients were enrolled in the study. The majority of the patients (50.3%) received oxaliplatin plus fluoropyrimidine as second-line treatment. The median progression-free survival and overall survival for the entire cohort were 2.5 months and 4.5 months, respectively. In univariate analyses, an Eastern Cooperative Oncology Group performance status ≥2, age ≥65 years, hypoalbuminemia, thrombocytosis, presence of metastatic peritoneal disease, elevated alkaline phosphatase and carcinoembryonic antigen levels, and a neutrophil-lymphocyte ratio (NLR) ≥3 were identified as poor prognostic factors. In multivariable analyses, low albumin level (p=0.031) and high NLR (p=0.05) were found to be independent prognostic factors for overall survival. **Conclusion:** Pancreatic cancer is a unique malignancy, and advanced disease has a dismal prognosis. In univariate analyses, we identified multiple factors that were poor prognostic variables. In particular, the albumin level and NLR were independent prognostic factors for overall survival, and these parameters might be useful in selecting the second-line treatment and predicting the survival of these patients.

Keywords: Chemotherapy; prognostic factors; pancreatic cancer; oxaliplatin, irinotecan

On a global scale, pancreatic cancer is a leading cause of cancer-related death. According to the GLOBOCAN data, approximately half a million people were diagnosed and died from pancreatic cancer in 2018.[1] The most prevalent histological subtype of pancreatic cancer is adenocarcinoma, with the cancer of the pancreatic head accounting for a majority of cases (60-70%). At the time of diagnosis, approximately 80-85% of individuals with pancreatic adenocarcinoma are ineligible for curative treatment.[2] Survival and response rates to treatment remain low due to the unique pathological features of pancreatic adenocarcinoma. Targeted therapies and immune checkpoint inhibitors that have shown efficacy in other types of cancer have not been significantly beneficial in advanced pancreatic cancer, except in indi-

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viduals with microsatellite-high tumors (MSI-H). Hence, chemotherapy continues to be the gold standard of treatment. Combination regimens, including multiple chemotherapeutic drugs, play a critical role in the frontline treatment of pancreatic adenocarcinoma and current guidelines recommend these as the first-line treatment for pancreatic cancer.[3-5] However, the median progression-free survival (PFS) with these combination regimens is less than seven months. In recent times, combination regimens such as nab-paclitaxel plus gemcitabine, nanoliposomal-irinotecan plus fluorouracil, and fluoropyrimidine plus oxaliplatin, as well as monotherapy with fluoropyrimidine and gemcitabine, have been recommended as second-line treatment for patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.[5-7] In addition to chemotherapy, pembrolizumab can be used in a patient who has tested positive for deficient mismatch repair or MSI-H.[8] Despite advancements in the second-line treatment of pancreatic cancer, survival and response rates remain low.

Although new studies are being conducted at a rapid pace, real-world data on outcomes of second-line treatment remain scarce; hence, additional data on real-world survival outcomes is necessary. Another critical aspect of pancreatic cancer research is determining predictive markers in individuals with advanced disease receiving second-line therapy. Few trials have evaluated the prognostic factors for patients undergoing second-line therapy. Hence, the goal of this study was to determine the survival outcomes following second-line treatment for pancreatic cancer and to evaluate prognostic markers in patients receiving second-line therapy.

MATERIAL AND METHODS

The trial involved individuals diagnosed with advanced pancreatic adenocarcinoma and the progression of the disease following first-line treatment. Patients' records were collected retrospectively from electronic databases maintained by the hospital at each of Türkiye's five oncology facilities. All included patients were above the age of 18 years, had metastatic disease with the progression of the disease following previous first-line treatment, and had detectable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The trial excluded patients who were lost to follow-up and did not receive any treatment following the progression of the disease after first-line chemotherapy.

We evaluated the prognostic significance of demographic characteristics, blood parameters, treatment received, and spread of the disease. Before initiating second-line treatment, all blood parameters were determined. The parameters analyzed included complete blood count, lactate dehydrogenase (LDH), albumin, carcinoembryonic antigen (CEA), and cancer antigen 19.9 (CA 19.9) levels. The threshold for neutrophil-lymphocyte ratio (NLR) was determined as 3, and patients were stratified as NLR<3 and NLR≥3. Serum albumin threshold was defined as 3.5 mg/dL, and patients were classified as albumin <3.5 and ≥3.5. The other parameters were classified as normal or "above the upper limit of normal" based on the cut-off values established by the local laboratories.

PFS was defined as the interval between the initiation of second-line treatment and RECIST-defined progression or death (PFS). overall survival (OS) was defined as the interval between the initiation of second-line treatment and death. Computed tomography (CT) or 18-fluorodeoxyglucose positron emission tomography-CT scans were used to evaluate tumor response according to the RECIST criteria. The objective response rates (ORR) were calculated by totalling the complete response and partial response rates.

Statistical Package for the Social Sciences (SPSS) Statistics 23 was used for statistical analysis. Wherever appropriate, categorical variables were compared using the chi-square or Fisher's exact test. The log-rank test was used to determine the prognostic effect of the investigated parameters on OS, and the Kaplan-Meier survival estimates were calculated. Cox regression analyses were performed to determine hazard assumptions. The proportional hazard assumption and model fit was assessed using residual analysis. A 5% Type-I error level was considered indicative of statistical significance. A p value of <0.05 was considered a statistically significant result.

The study was approved by the local ethics board (Ankara University, Faculty of Medicine, Clinical Research Ethics Committee; date: May 27, 2019; no: 10-799-19) according to good clinical practice and applicable laws, and the Declaration of Helsinki.

RESULTS

In all, 161 patients who received second-line treatment were enrolled in the study. The median age was 59 years (minimum-maximum: 30-79). The most common location of the tumor was the head of the pancreas (56%). Thirty-one percent of patients were female, and 68.3% were male. When second-line therapy was initiated, the majority of patients had an ECOG performance status of 0 or 1.

Most of the patients (50.3%) received oxaliplatin-based chemotherapy as the second-line treatment. The other treatment regimens were capecitabine (12.4%), gemcitabine (6.8%), and a combination of gemcitabine plus cisplatin (6.2%). Patients received a median of three cycles of chemotherapy. Disease progression was the most common reason (63.8%) for treatment discontinuation. Other causes for discontinuation were completion of the planned therapy cycle (28.1) and drug toxicities (7.8%). The patient characteristics and treatment regimens are shown in Table 1.

At the time of data cut-off, the median follow-up duration was 4.5 months (minimum-maximum: 0.1-67 months). The median PFS was 2.5 months (2.12-3.04), and the median OS was 4.5 months (3.8-5.1) (Figure 1, 2). The median OS from the time of diagnosis was 12 months (10.7-13.2). The ORR following second-line therapy was 7.4%, and the clinical benefit rate (CBR) of second-line therapy was 27.5%. There was no statistically significant difference in OS between the different treatment regimens (p=0.44). In patients who received combination regimens, the median OS was 4.6, 5.2, and 3 months in the subgroups with ECOG 0, 1, and ≥2, respectively. The median OS of patients who received monotherapy was 4.7, 5.1, and 2.7 months in subgroups with ECOG performance status 0, 1, and ≥2, respectively.

In univariate analyses, the median OS was found to be significantly longer in patients with high albu-

TABLE 1: Patient characteristics and second-line treatment regimens.

Parameter	Value
Age (median, minimum-maximum)	59 (30-79)
Sex (%)	
Male	68.3
Female	31.7
Tumor localization (%)	
Head	56
Corpus	26
Body	18
ECOG performance status (%)	
0	26.1
1	39.8
2	28.6
3	5.6
Metastatic sites (med, minimum-maximum)	2 (1-10)
Metastatic sites (%)	
Liver	78.8
Lung	31.1
Peritoneal	22.9
Lymph node	20.4
Bone	12.2
Ascites	19.9
Treatment regimens (n, %)	
Oxali plus fluoropyrimidine	81 (50.3)
Capecitabine	20 (12.4)
Gemcitabine plus cisplatin	10 (6.2)
Gemcitabine	11 (6.8)
FOLFIRI	6 (3.7)
FOLFIRINOX	2 (1.2)
Nab-paclitaxel	3 (1.9)
Other	19 (17.4)

ECOG: Eastern Cooperative Oncology Group.

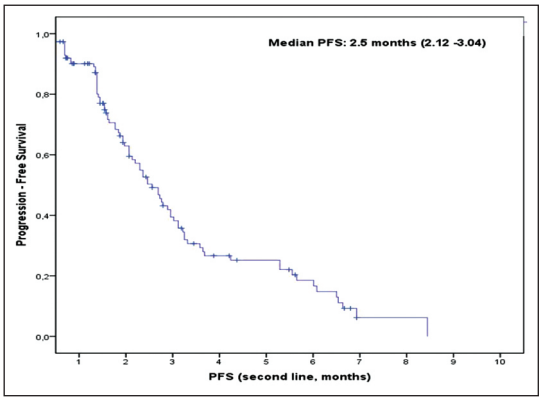

FIGURE 1: Progression-free survival with second-line chemotherapy. PFS: Progression-free survival.

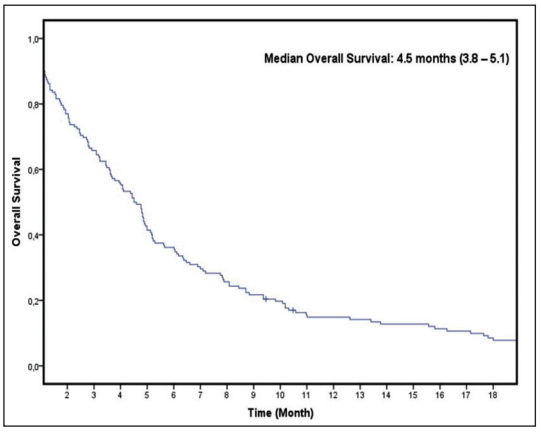

FIGURE 2: Overall survival with second-line chemotherapy.

min level, normal alkaline phosphatase (ALP) level, ECOG 0-1, normal CEA levels, advanced age (≥65), increased thrombocyte count, and low NLR (Table 2).

In multivariate analyses, low albumin level and high NLR were found to be statistically significant (p=0.031 for albumin and p=0.05 for NLR) and independent factors for OS. The risk of death was 1.7 times higher in patients with an albumin level of less than 3.5 mg/dL. Additionally, the risk of death was 1.66 times higher in patients with NLR≥3 (Table 3).

DISCUSSION

In our study, the median PFS and OS following second-line therapy were 2.5 and 4.5 months, respectively. The ORR and CBR were 7.4% and 27.5%, respectively. OS between the various second-line chemotherapy regimens showed no statistically significant difference. Age, albumin, ALP, ECOG PS, CEA level, and NLR were found to be prognostic variables for OS in the univariate analysis for second-line treatment. In multivariate analysis, low albumin and high NLR were associated with a poor prognosis for OS.

Combination therapy such as nab-paclitaxel plus gemcitabine, nano-liposomal-irinotecan plus fluorouracil, or fluoropyrimidine plus oxaliplatin might be recommended for patients with ECOG status 0 and 1. According to the final results of the NAPOLI-1 study, the median OS with nano-liposomal-irinotecan plus fluorouracil therapy was 6.2 months. The median PFS and ORR were reported to be 3.1 months and 17%, respectively.[9] AGEO was a prospective multicenter cohort trial, and the median OS and PFS with nab-paclitaxel plus gemcitabine were 8.8 and

TABLE 2: Univariate analyses for overall survival.

Parameters	Patients (n)	Overall survival (Median-months)	p value
Age (years)			
<65	118	4.8	**0.015**
≥65	34	2.7	
Albumin (mg/dL)			
<3.5	52	2.7	**<0.001**
≥3.5	55	6.4	
ALP			
Normal	48	5.1	**0.03**
High	63	3.4	
ECOG-PS			
0-1	97	5.2	**<0.001**
≥2	50	2.7	
CEA			
Normal	21	7.7	**0.01**
High	83	3.4	
CA 19.9			
Normal	27	4.9	0.62
High	86	3.6	
LDH			
Normal	67	3.9	0.32
High	25	3.6	
Thrombocytosis			
Yes	24	4,5	0.068
No	110	3,5	
Anemia			
Yes	78	4.3	0.81
No	42	3.9	
NLR			
<3	53	6.89	**<0.001**
≥3	61	3,2	
Presence of ascites			
Yes	31	3.2	**0.038**
No	120	4.8	
Liver metastasis			
Yes	96	3.6	0.21
No	24	4.5	

ALP: Alkaline phosphatase; ECOG-PS: Eastern Cooperative Oncology Group-performance status; CEA: Carcinoemriogenic antigen; CA 19.9: Cancer antigen 19.9; LDH: Lactate dehydrogenase; NLR: Neutrophil-lymphocyte ratio.

TABLE 3: Multivariate analyses for overall survival.

Parameter	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
NLR	**0.05**	1.666	0.975	2.848
CEA	0.908	0.964	0.512	1.812
ALP	0.141	0.686	0.416	1.133
Presence of ascites	0.590	0.873	0.533	1.430
Albumin	**0.031**	1.741	1.053	2.878
Age	0.238	0.712	0.405	1.252
ECOG-PS	0.263	0.746	0.446	1.247

CI: Confidence interval; NLR: Neutrophil-lymphocyte ratio; CEA: Carcinoemriogenic antigen; ALP: Alkaline phosphatase; ECOG-PS: Eastern Cooperative Oncology Group-performance status.

5.1 months, respectively, in patients who received frontline FOLFIRINOX.[7] Oxaliplatin or irinotecan with fluorouracil combinations is indicated for patients with ECOG 0 and 1. These combination regimens have been shown to have a comparable OS and PFS. The median OS and PFS with oxaliplatin or irinotecan plus fluorouracil combinations were reported to be 5-6 months and 2.5-3 months, respectively.[10-12] In our analysis, we found that the median OS was 4.6 months. In the patient groups with ECOG 0-1 and ≥2, the median OS was 5.2 months and 3 months, respectively. Since the majority of patients received oxaliplatin plus fluoropyrimidine and there were no patients who received nab-paclitaxel or nanoliposomal irinotecan combination therapy, the median OS was found to be shorter than in the NAPOLI-1 and AGEO trials. However, our results were comparable with the outcomes of trials in which fluoropyrimidine-based combination regimens were administered.

Monotherapy is another treatment option for advanced pancreatic cancer, particularly in patients with an ECOG PS 2 or above. Numerous studies evaluating various chemotherapeutic drugs as monotherapy have been published, including those evaluating nab-paclitaxel, oxaliplatin, S1, irinotecan, nano-liposomal irinotecan, gemcitabine, pemetrexed, and capecitabin.[13] Median OS was reported to be 3.5 to 7.3 months with these agents in patients whose ECOG status was 0-1 or ≥2.[13-17] The median OS in our study was 4.7 months, which is consistent with the results of previous studies. About 30% of individuals who received monotherapy had an ECOG performance status ≥2. As indicated previously, this rate is higher than that in earlier trials. Bittoni et al. presented real-world data on second-line treatment for pancreatic cancer.[18] The OS and PFS were 5.26 months and 2.76 months, respectively, and our results are in line with these outcomes.

To our knowledge, there are currently no real-world data comparing the outcomes of combination regimens in the second-line therapy of advanced pancreatic cancer. We found no difference in outcomes between the various treatment regimens. However, the number of patients who received new generation chemotherapeutic agents as combination or monotherapy was relatively low, and this might have influenced the outcomes. This was one of the limitations of our study.

Few trials evaluating the prognostic variables in patients with advanced pancreatic cancer receiving second-line therapy have been published. In the first trial, it was revealed that ECOG, CA 19.9, and LDH levels were independent predictors of OS in 144 patients receiving second-line therapy.[18] Pokataev et al. reported that a Karnofsky performance status of ≤70% and an NLR>5 were independent poor prognostic indicators for OS in patients with advanced pancreatic cancer receiving second-line therapy.[19] In the most comprehensive study, which included approximately 400 patients and evaluated 50 parameters, age, smoking and performance status, liver metastases, ascites, pain, jaundice, duration of first-line treatment, and type of treatment regimen were identified as independent prognostic factors for OS.[20] Age, albumin level, ALP level, ECOG PS, CEA level, and NLR level were determined as prognostic factors for OS in our trial. Additionally, in multivariate analysis, low albumin and a high NLR were found to be poor prognostic factors for OS. Despite some discrepancies between our findings and those from the earlier studies, most of the factors identified as prognostic markers are consistent with those identified in previous trials. It is well established that inflammation can have a detrimental effect on the outcomes and responsiveness to treatment in several types of cancers. NLR can be used to determine the

severity of an inflammatory condition. In previous trials, it was shown that a high NLR level, which might indicate a greater degree of inflammation, was associated with worse outcomes in several types of cancer.[21-23] Also, consistent with the previous research, we demonstrated that a high NLR represents an independent poor prognostic factor for OS. Albumin is a negative acute-phase protein that also indicates the nutritional condition of the body. Both inflammation and malnutrition can affect albumin levels. In a recent trial, the albumin level was found to be a predictive factor for OS in patients with advanced pancreatic cancer who received frontline treatment.[24] In our study, albumin was found to be an independent prognostic factor. This finding could be explained by an increased inflammatory state and nutritional deficiency.

The major limitations of our trial include the retrospective design, relatively small number of patients enrolled, and a limited number of patients treated with next-generation chemotherapeutic drugs (nab-paclitaxel, nano-liposomal irinotecan, etc.) as combination or monotherapy. Nevertheless, multicenter outcomes of the real-world experience in 161 patients are the major highlight of our trial.

CONCLUSION

In conclusion, we showed that real-world data were consistent with clinical trial findings. Despite recent advancements in pancreatic cancer treatment, survival and response rates remain poor. Nonetheless, numerous studies on the novel therapeutic targets are ongoing. The outcomes of these studies might influence the first-and second-line treatment regimens. Additionally, treatment strategies might be modified considering the prognostic markers identified in previous trials.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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