Prognostic Significance of Glyoxalase-1 Enzyme Activity in Metastatic Pancreatic Cancer Patients

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ABSTRACT

In previous studies, excessive expression of Glyoxalase-1 enzyme (GLO-1) has been reported in various tumor tissues and cells, and it has been shown to be associated with poor prognosis in some tumors. In this study, we examined the relationship between GLO-1 expression, progression-free survival (PFS) and metastatic overall survival (mOS). We retrospectively appraised 99 patients diagnosed with metastatic pancreatic adenocarcinoma from July 2012 to August 2020. GLO-1 expression was assessed by immunohistochemistry. According to the immunoreactivity score, the patients were divided into two groups: those with low immunoreactivity and those with high immunoreactivity. Survival probabilities were predicted with the Kaplan-Meier method and group comparisons were applied with the Log-rank test. Furthermore, univariate and multiple Cox regression analyses were used to determine the most substantial risk elements. While the median PFS was 3 months (95% CI: 1.84-4.16) in the low GLO-1 IRS group, the median PFS was 2 months (95% CI: 1.76-2.24) in the group with high GLO-1 IRS (p= 0.002). While the median mOS was 7 months (95% CI: 6.39-7.61) in the group with low GLO-1 IRS, the median mOS was 5 months (95% CI: 3.72-6.28) in the group with high GLO-1 IRS (p< 0.001). According to multivariate analysis; a low GLO-1 immunoreactivity score was the independent variable for good mOS (HR= 0.51; 95% CI: 0.33-0.79, p= 0.003) and PFS (HR= 0.64; 95% CI: 0.42-0.97, p= 0.035). In conclusion, increased GLO-1 expression was associated with a poor prognosis in metastatic pancreatic cancer patients.

Keywords: Glyoxalase 1, Pancreatic cancer, Prognosis

INTRODUCTION

While exocrine pancreatic cancer is relatively rare, a significant proportion of patients have advanced disease at the time of diagnosis. Worldwide, pancreatic cancer is the sixth most common cause of cancer-related deaths.[1] Even in node-negative patients with optimally resected tumours, the 5-year survival rate is around 20%.[2] Despite current treatment approaches, survival outcomes in pancreatic cancer are unsatisfactory.

Systemic chemotherapy for metastatic disease is palliative, not curative. However, evidence from randomised trials[3-6] suggest that systemic chemotherapy may improve symptoms and prolong survival compared to the best supportive care alone. Identifying patients who may benefit from palliative chemotherapy will reduce the costs and side effects associated with ineffective treatment and improve survival.

In the 1920s, Warburg discovered high levels of aerobic glycolysis in tumour tissue.[7] Glyoxal-1 enzyme (GLO-1), a part of the cytosolic glyoxalase system present in all human cells, is involved in glutathione removal of methylglyoxal (MG) and endogenous reactive dicarbonyl metabolites.[8]

Excessive accumulation of methylglyoxal and endogenous reactive dicarbonyl metabolites in a cell disrupts cell replication and leads to apoptosis. Therefore, while GLO-1 expression acts as a tumour suppressor protein in non-malignant cells by preventing protein and DNA degradation and apoptosis, increased GLO-1 activity in malignant cells with high glycolytic activity is thought to inhibit tumour apoptosis, leading to tumour tissue growth and multidrug resistance.[9]

Previous studies have reported increased GLO-1 expression in various tumour tissues and cells.[10-12] This has been shown to be linked to adverse prognosis in a variety of tumours including oropharyngeal squamous cell carcinoma, prostate cancer and breast cancer.[13-15]

The aim of this report was to investigate the relationship between GLO-1 expression,PFS and mOS during first-line palliative chemotherapy in patients with advanced pancreatic cancer.

PATIENTS AND METHODS

Patient Assignment

Following the ethical approval patients diagnosed with pancreatic cancer who were followed up and treated at the Oncology Department of Erciyes University between July 2012 and August 2020 were recruited.

Patients with histopathologically advanced pancreatic cancer, patients receiving first-line chemotherapy, and patients with complete clinical records including demographic information, pathology and treatment modalities were included in the study.

Patients with a pathological diagnosis of non-adenocarcinoma, non-metastatic, under 18 years of age and with a second malignant neoplasm confirmed at different sites were excluded. 99 patients were included. Patient records were retrospectively reviewed and possible prognostic factors such as sex (male/female), performance status, age, site and number of metastases, haematological parameters (haemoglobin), biochemical parameters (lactate dehydrogenase, albumin) and chemotherapies received were derived from the medical records. Paraffin blocks of the patients selected for immunohistochemical staining were obtained from the pathology archive of Erciyes University.

Immunohistochemistry

For GLO-1 immunohistochemistry, 5 μm thick sections were prepared from paraffin blocks of selected patients. Tissue samples were placed on positively charged poly-L-lysine slides and placed in an oven at 56-60°C overnight for initial deparaffinisation. Immunohistochemistry of the sections was then realised on a fully automated immunohistochemistry instrument (Ventana Benchmark/ Ultra, Ventana Medical Systems, USA), which fulfils all staining steps, including antigen retrieval, under constant temperature and conditions. GLO-1 polyclonal antibody (retreatment with EDTA for 20 min, dilution 1/50, incubation for 120 min, LS-Bio Glyoxalase-1 Rabbit anti-human polyclonal antibody LS-C98388) was applied to the sections as the primary antibody and the targeted proteins were visualised. After washing, the sections were rehydrated by passing through increasing gradient alcohol solutions. The air-dried sections were kept in xylene for 15 minutes and coverslipped with entellan. Immunohistochemically stained sections were graded by an independent pathologist (K.D.) relative to staining intensity (0= no staining, 1= weak staining, 2= moderate staining, 3= strong staining) in accordance with grading methods used in previous studies[13,16] (Figure 1). As most of the sections examined were biopsy samples, the percentage of positive tumour cells was not taken into account. The immunoreactivity score (IRS) was divided into two groups as low (0-1) and high (2-3).

Ethical Approval was granted by Clinical Research Ethics Committee of Erciyes University (Decision No: 2020/384).

Statistical Analysis

Histograms and q-q plots were used to determine the distribution of the data. Descriptive statistics were indicated as numbers, percentages and means. Fisher's exact test and Pearson chi-squared test were employed to assess the relation between categorical factors. Progression-free survival (PFS) was calculated by recording the time from the start of first-line chemotherapy to the date of progression in months. Metastatic overall survival (mOS) was calculated by recording the time from the start date of first-line chemotherapy to the date of death or last follow-up in months. Risk factors

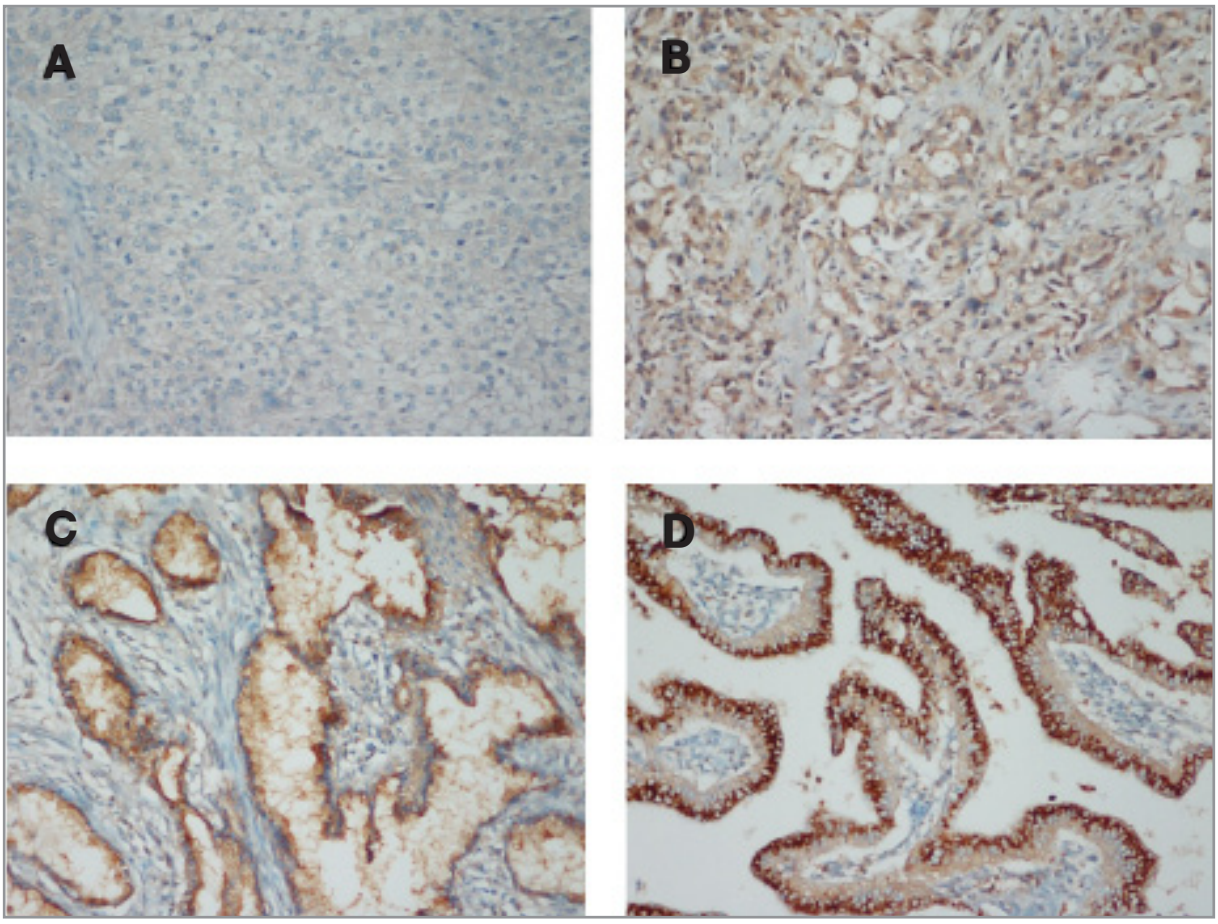

Figure 1. Immunohistochemical staining with Anti-GLO-1 antibody (brown signal) of tumor tissue blocks of patients with metastatic pancreatic adenocarcinoma. **A:** no staining, **B:** weak, **C:** moderate, **D:** strong

for PFS and mOS were identified using univariate and multivariate Cox regression analysis. The Kaplan-Meier method was applied to determine the probability of PFS and mOS, and the log-rank test was performed for group comparisons. The hazard ratio (relative risk) was obtained by taking the 95% confidence interval, and a $p< 0.05$ was considered for statistical significance. SPSS 22 software was employed for all analyses.

RESULTS

The study included 99 patients with metastatic pancreatic adenocarcinoma (mPC), 64 (64.6%) men and 35 (35.4%) women. The median age of the patients was 62 years (32-86 years). The most common site of metastasis was liver in 82 (82.8%) patients, followed by lung in 21 (21.2%) patients, nonregional lymph nodes in 19 (19.2%) patients, peritoneal in 12 (12.1%) patients and bone in 8 (8.1%) patients. First-line chemotherapy; 64 patients received cisplatin+gemcitabine, 14 patients received FOLFIRINOX (Oxaliplatin + Leucovorin + Irinotecan + Fluorouracil), 21 patients received other chemotherapies (single-agent gemcitabine, gemfufol, nab-paclitaxel, gemcitabine+5 Fluorouracil). Chemotherapy responses; 58 (58.6%) patients had progressive disease, 25 (25.2%) patients had stable disease, 16 (16.2%) patients had a partial response.

GLO-1 IRS was high in 48 (48.5%) patients and low in 51 (51.5%) patients. According to GLO-1 IRS, there was no significant difference in clinicopathological factors such as sex (male/female), age, performance status, number of metastatic sites, haematological parameters (haemoglobin), biochemical parameters (lactate dehydrogenase, albumin) and chemotherapies (Table 1).

Table 1. Characteristics of participants according to GLO-1 IRS

Variable	GLO-1 IRS		p
	Low	High	
Gender			
Female	22 (43.1)	13 (27.1)	0.140
Male	29 (56.9)	35 (72.9)	
Age (years)			
< 65	33 (64.7)	29 (60.0)	0.683
≥ 65	18 (35.3)	19 (40.0)	
ECOG performance status			
0	16 (31.4)	15 (31.2)	1.000
1-2	35 (68.6)	33 (68.8)	
Number of metastatic sites, n (%)			
Single site	35 (68.6)	27 (56.3)	0.220
Multiple	16 (31.4)	21 (43.7)	
Chemotherapy			
FOLFIRINOX	8 (15.7)	6 (12.5)	0.171
Cisplatin + Gemcitabine	36 (70.6)	28 (58.3)	
Other*	7 (13.7)	14 (29.2)	
Chemotherapy Responsea			
PD	26 (51.0)	32 (66.7)	0.153
SD + PR	25 (49.0)	16 (33.3)	
Hemoglobin**			
Normal	33 (66.0)	33 (68.8)	0.831
Anemia	17 (34.0)	15 (31.2)	
Lactate dehydrogenase (LDH)***			
< ULN	36 (75.0)	30 (62.5)	0.271
≥ ULN	12 (25.0)	18 (37.5)	
Albumin			
< 4 g/dL	25 (50.0)	20 (42.6)	0.543
≥ 4 g/dL	25 (50.0)	27 (57.4)	

** Other (single-agent gemcitabine, gemfufol, nab-paclitaxel, gemcitabine+5 Fluoro Uracil) ** Lower limits of reference range: men, 13.0 g/dL; women, 11 g/dL; *** Upper limit of reference range: 250 U/L*
***Abbreviations**: FOLFIRINOX (Oxaliplatin + Leucovorin + Irinotecan + Fluorouracil); PD: Progressive disease, SD: Stable disease, PR: Partial response; ULN: Upper limit of normal; ECOG: Eastern Cooperative Oncology Group*

In patients with high GLO-1 IRS, 66.7% had progression and 33.3% had stable disease or partial response to first-line chemotherapy; in patients with low GLO-1 IRS, 51.0% had progression and 49.0% had stable disease or partial response (Table 1).

Univariate analysis was performed to evaluate the relationship between PFS and clinicopathological variables (gender, age, performance status, number of metastatic sites, haematological parameters (haemoglobin), biochemical parameters (lactate dehydrogenase, albumin), chemotherapies and GLO-1 immunoreactivity score). According to the results of univariate analysis, chemotherapy (FOLFIRINOX) (p= 0.029, p= 0.006) and low GLO-1 immunoreactivity score (p= 0.014) were significantly correlated with longer PFS. No statistically significant correlation was found with other variables (Table 2).

When evaluated by multivariate analysis; low GLO-1 immunoreactivity score was an independent variable for extended PFS (HR= 0.64; 95 % CI: 0.42-0.97, p= 0.035); and patients receiving folfirinox as chemotherapy was an independent variable for longer PFS (HR= 2.01; 95% CI: 1.05-3.87, p= 0.036), (HR= 2.57; 95% CI: 1.20-5.50, p= 0.015) (Table 2).

On univariate analysis for mOS, chemotherapy (FOLFIRINOX) (p= 0.034, p= 0.013) and low GLO-1 immunoreactivity score (p= 0.001) were significantly related to high mOS. No statistically significant correlations were found with other variables (Table 3).

Table 2. Univariate and multiple cox regression analysis of variables for PFS

Variable	Univariant p	Multivariant HR (95% CI)	p
Age, years			
< 65 / ≥ 65	0.409	-	-
Gender			
Male/ Female	0.941	-	-
ECOG PS			
0 / 1-2	0.540	-	-
Chemotherapy			
FOLFIRINOX		1	
Cisplatin+Gemcitabine	0.029	2.01 (1.05-3.87)*	0.036
Other	0.006	2.57 (1.20-5.50)*	0.015
Number of metastatic sites			
Single/Multiple	0.206	-	-
Hemoglobina			
Normal/Anemia	0.941	-	-
LDH			
< ULN / ≥ ULN	0.958	-	-
Albumin			
< 4 dL / ≥ 4 dL	0.225	-	-
GLO-1 IRS			
Low		1	
High	0.014	1.57 (1.03-2.39)*	0.035

** Only variable that remained in the multiple mode, ** Other (single-agent gemcitabine, gemfufol, nab-paclitaxel, gemcitabine+5 Fluoro Uracil)*
Abbreviations: *CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; FOLFIRINOX (Oxaliplatin + Leucovorin + Irinotecan + Fluorouracil), ULN: Upper limit of normal, GLO-1 IRS: Glyoxalase-1 immunoreactivity score (staining intensity 0-1: low, 2-3: high)*

On multivariate analysis, only low GLO-1 immunoreactivity score was an independent variable for high mOS (HR= 0.51; 95% CI: 0.33-0.79, p= 0.003) (Table 3).

According to Kaplan-Meier analysis, median PFS was 3 months (95% CI: 1.84-4.16) in the GLO-1 IRS low group and 2 months (95% CI: 1.76-2.24) in the GLO-1 IRS high group (p= 0.002) (Figure 2). Median mOS was 7 months (95% CI: 6.39-7.61) in the GLO-1 IRS low group and 5 months (95% CI: 3.72-6.28) in the GLO-1 IRS high group (p< 0.001) (Figure 3).

DISCUSSION

Pancreatic cancer is among the malignancies with aggressive behavior. Although current treatments are applied to these patients, survival is not at the desired level.[17] There is not enough markers to show the disease course and treatment response in pancreatic cancer. Therefore, the need for predictive and prognostic markers is increasing in patients with metastatic pancreatic cancer.

GLO-1 is the first and rate-restrictor catabolic enzyme in the breakdown pathway of MG, a highly reactive intermediate of glycolysis known to be the main premise of advanced glycation end products.[18] In many types of malignancies, enhanced expression and activity of GLO-1 had a preventive impact on cells against the toxicity of anticancer agents. This protective effect promoted survival and MDR in more invasive and aggressive cells, ultimately leading to treatment failure.[19]

GLO-1 has a critical role as a pro-survival element in the protection of cancer cells from apoptosis. Mechanistically, by sustaining the levels of MG inevitably produced throughout malignant tumour development, GLO-1 regulates mitochondrial apoptotic mechanisms. So, rather than directly modulating malignant tumour cell proliferation and growth, GLO-1 affects survival by preventing apoptosis.[20,21] Reduced GLO-1 induces apoptosis in

Table 3. Univariate and multiple cox regression analysis of variables for mOS

Variable	Univariant p	Multivariant HR (95% CI)	p
Age, years			
< 65 / ≥ 65	0.145	-	-
Gender			
Male/ Female	0.464	-	-
ECOG PS			
0 / 1-2	0.381	-	-
Chemotherapy			
Folfirinox		1	
Sisplatin+Gemsitabin	0.034	2.02 (0.95-4.29)*	0.068
Other	0.013	2.27 (0.99-5.23)*	0.054
Number of metastatic sites			
Single/Multiple	0.467	-	-
Hemoglobina			
Normal/Anemia	0.694	-	-
LDH			
< ULN / ≥ ULN	0.077	-	-
Albumin			
< 4 / ≥ 4	0.070	-	-
GLO-1 IRS			
Low		1	
High	0.001	1.97 (1.26-3.08)*	0.003

** Only variable that remained in the multiple mode, ** Other (single-agent gemcitabine, gemfufol, nab-paclitaxel, gemcitabine+5 Fluoro Uracil)*
Abbreviations: *Abbreviations son hali: CI: Confidence interval; HR: Hazard ratio; mOS: metastatic overall survival; ECOG PS: Eastern Cooperative Oncology Group performance status; FOLFIRINOX (Oxaliplatin + Leucovorin + Irinotecan + Fluorouracil), ULN: Upper limit of normal, GLO-1 IRS: Glyoxalase-1 immunoreactivity score (staining intensity 0-1: low, 2-3: high)*

human epidermal squamous cell carcinoma cells in the existence of tumour necrosis factor-related apoptosis-inducing ligand, inhibiting both migration and invasion.[22] In advanced stage prostate cancer, the immunosuppressive microenvironment sustained by GLO-1 hyperexpression mediates 5-hydro-5-methylimidazolone-mediated upregulation of the immune checkpoint protein programmed death ligand 1, which promotes malignant tumour progression.[23] These insights clearly indicate that GLO-1 is an important determinant in the proliferation and survival of tumour cells in diverse types of malignant tumours, which are related to a worse prognosis for patients.

Although increased expression of GLO-1 has been reported in cancers[11,21,24], a limited number of studies have evaluated its association with survival.[13,14,15,25] Kreycy et al. found that high and nuclear Glyoxalase-1 staining was significantly associated with worse progression-free and disease-specific survival and was an independent predictor of poor outcome in patients with oropharyngeal squamous cell carcinoma.[13] Burdelski et al., reported that GLO-1 overexpression was substantially correlated with adverse tumour phenotype including advanced stage, high Gleason grade, nodal involvement and early biochemical recurrence.[14] Peng et al., confirmed that in breast cancer patients, those with high GLO-1 expression had worse OS and recurrence-free survival (RFS) than those with low GLO-1 expression. They also demonstrated that GLO-1 expression is an independent prognostic variable for both OS and RFS in breast cancer patients in multivariable analysis.[15]

Cheng WL, et al., reported that increased expression of GLO-1 was strongly related to gastric wall invasion, lymph node involvement and pathological stage, indicating a distinct function of GLO-1 in gastric cancer development and progression. The 5-year survival rate of the groups with low levels of GLO-1 expression was substantially higher than that of the groups with high levels of expression.[25]

In our study, high GLO-1 staining was significantly associated with decreased PFS (2 months

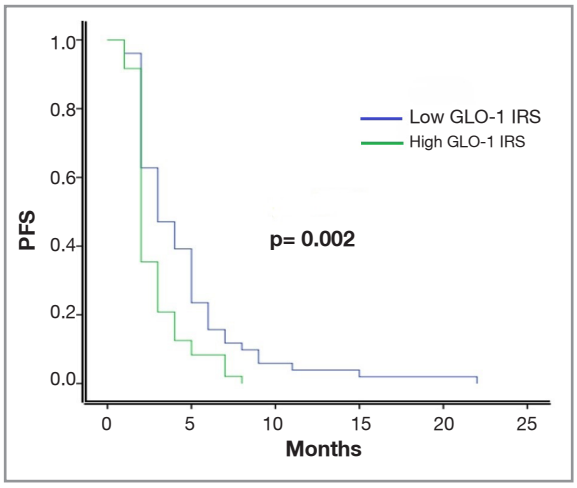

Figure 2. Kaplan–Meier curves of PFS based on GLO-1 IRS

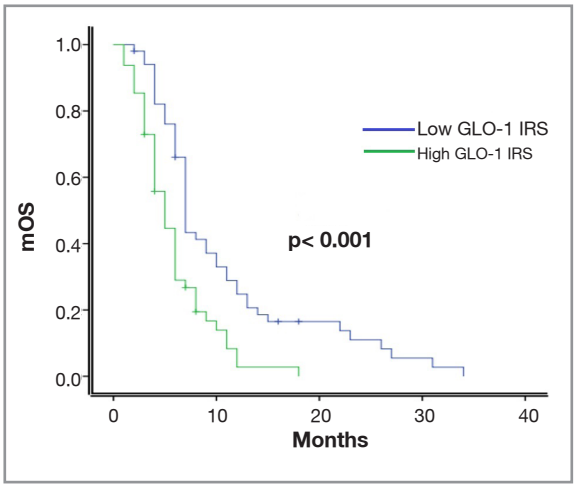

Figure 3. Kaplan– Meier curves of mOS based on GLO-1 IRS

vs. 3 months, p= 0.002) and mOS (5 months vs. 7 months, p< 0.001) compared to low GLO-1 staining in patients with metastatic pancreatic cancer. Moreover, multivariate analysis indicated that a high Glyoxalase-1 staining was an independent indicator of both PFS (HR= 0.64, 95%; CI: 0.42-0.97, p= 0.035) and mOS (HR= 0.51, 95%; CI: 0.33-0.79, p= 0.003) .

Crake et al., found an association between GLO-1 upregulation and gemcitabine resistance in pancreatic cancer cell lines.[26] In a study of anticancer drugs, increased GLO-1 expression was shown to be associated with multidrug resistance.[27] In our study, when we analysed the patients in terms of chemotherapy response, there was no significant difference between the two high/low GLO-1 expression groups in terms of the type of chemotherapy received, but the progression rate was higher in the high GLO-1 expression group, but this was not statistically significant. This may be due to the retrospective nature of the study and the relatively small number of patients.

In patients with metastatic pancreatic cancer, chemotherapy regimens such as FOLFIRINOX, gemcitabine + nab-paclitaxel, and gemcitabine + cisplatin for patients with BRCA1/2 and PALB2 mutations are preferred in the first-line setting.[28] Compared with gemcitabine, FOLFIRINOX has been shown to be linked to better response rate, PFS and OS.[3] In a meta-analysis comparing FOLFIRINOX with nab-paclitaxel/gemcitabine, the overall risk of death and disease progression was similar, despite the numerically longer mOS with FOLFIRINOX .[29] In our study, FOLFIRINOX was linked to longer PFS and mOS compared to other chemotherapy regimens in univariate analysis.

There are certain restrictions to this study. The first limitation is that the sample was relatively small, retrospective, non-randomised and from a single centre in Turkey, which may lead to incorrect generalisation of the results. Secondly, Immunohistochemically stained sections were not reviewed by a second independent pathologist. Finally, the level of GLO-1 expression was not compared to normal pancreatic tissue.

Conclusion

The presented data observed that increased GLO-1 expression was related to poor prognosis. Detection of a high GLO-1 staining pattern could be employed in future clinical studies to determine metastatic pancreatic cancer patients with a high risk for treatment failure. In addition, GLO-1 may be a potential target for future specific therapies.

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