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Neutrophil-to-lymphocyte ratio as a prognostic factor in patients during palliative treatment of pancreatic ductal adenocarcinoma with a FOLFIRINOX regimen

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Introduction. Difficulties in advanced pancreatic ductal adenocarcinoma (PDAC) treatment require a constant search for novel prognostic factors. The aim of this study is to determine the role of various morphological parameters in predicting the prognosis of advanced PDAC during systemic therapy with a FOLFIRINOX regimen.

Material and methods. The data of 52 patients, treated with FOLFIRINOX chemotherapy due to metastatic PDAC were analyzed retrospectively in this study.

Results. The median time of overall survival (OS) in the group of patients with neutrophil-to-lymphocyte ratio (NLR) ≥3 was 5.8 months, compared to 14.5 months in patients with NLR < 3. Median progression-free survival (PFS) in patients with NLR ≥ 3 was 4.1 months, compared to 8.5 months in patients with NLR < 3. There were no statistically significant differences among patients concerning the lymphocyte-to-monocyte ratio (LMR) and platelets-to-lymphocyte ratio (PLR).

Conclusions. Higher NLR is a negative prognostic factor in metastatic PDAC.

Key words: pancreatic ductal carcinoma, chemotherapy, overall survival, time to progression, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelets-to-lymphocyte ratio

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most aggressive cancers with increasing rates of incidence and mortality. It is estimated that PDAC will be the second cause of death among oncological patients in USA by 2030 [1]. Among Polish patients, PDAC was the cause of death in 5000 cases, and was diagnosed in 3837 patients in 2018 [2].

Despite the progress in diagnosis and treatment, PDAC remains a disease with poor survival. Even with radical treatment including surgical approach and adjuvant systemic therapy, the median overall survival does not exceed 5 years.

In metastatic PDAC, multi-drug regimens such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, levofolic/folinic acid), gemcitabine with nab-paclitaxel or gemcitabine in monotherapy are recommended in systemic therapy [3–5]. The FOLFIRINOX regimen was compared to gemcitabine in monotherapy in Connroy study, which included advanced PDAC without a previous history of treatment. The median time of overall survival in the group of patients treated with the FOLFIRINOX regimen was 11.1 months, compared to 6.8 months in the gemcitabine group. Adverse effects of used therapy were more common during treatment with FOLFIRINOX regimen, although it did not significantly affect patients quality of life [6].

In the study comparing gemcitabine in monotherapy to gemcitabine accompanied by nab-paclitaxel, OS was 6.7 months compared to 8.5 months in the two-drug regimen [7].

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Limited effectiveness of the systemic approach in PDAC treatment might be caused by the microenvironment surrounding the growing tumor. The desmoplastic response of surrounding tissues and low angiogenesis are the cause of inadequate chemotherapy effects [8]. Besides relative drug resistance, PDAC might avoid the systemic immunological response. This phenomenon is related to the presence of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSC), and regulatory T-cells activated by TGF beta. Those cells are able to inactivate CD4+ and CD8+ lymphocytes, dendritic cells, NK cells, and macrophages [9]. This might be the reason for the poor effects of immunotherapy trials in PDAC. With increasing knowledge about the role of immunological response and inflammation in tumor tissue, more studies concerning prognostic factors based on immunological cells are being published. Those prognostic factors include the neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). Increased NLR is considered a poor prognosis factor in renal cell carcinoma, malignant melanoma, metastatic colorectal cancer or non-small cell lung cancer [10, 11].

The aim of this study was to determine the role of NLR, PLR, LMR as prognostic factors in patients treated with FOLFIRINOX chemotherapy in metastatic PDAC.

Material and methods

There were 52 patients who were enrolled for this study. We have included the patients who were undergoing systemic treatment with the FOLFIRINOX regimen due to metastatic PDAC between 2017 and 2021. Inclusion criteria contained a PDAC diagnosis in clinical stage IV, systemic treatment with the FOLFIRINOX regimen. We have collected demographic data such as the patients' sex, age, height, weight, results of CBC tests, progression-free survival time in months, overall survival in months, and localization of metastases. Parameters such as NLR, PLR and LMR were based on CBC results.

The CBC was assessed at the day of the treatment initiation, before the start of systemic therapy.

The overall survival- and progression-free figures were calculated by subtracting the date of the metastatic disease diagnosis from the date of death and disease progression, respectively for complete observations or from the date of the last follow-up for censored observations. The cut-off values for NLR, PLR, and LMR were pre-set, based on current literature. The log rank test was used for comparing the survival between two groups. The relationships between quantitative variables were analyzed using the Spearman's rank correlation coefficient. The analysis was performed using STATISTICA 13.3 software (TIBCO software). The $p < 0.05$ values were considered significant. Inclusion criterium was an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The observed cohort of patients comprised 25 male (48%) and 27 female (52%). The median age of patients was 62 years (range from 31 to 72 years).

The most common metastases localizations were liver (39 patients – 75%) and peritoneum (5 patients – 9.6%). Lungs were the localization of single metastases in 1 patient (2%) and multi-organ metastatic disease was observed in 5 patients (9.6%). The reason for termination of treatment was disease progression (41 patients – 79%) and adverse effects of treatment (4 patients – 8%). There are 4 patients still being observed during observation and 3 patients have been lost to follow-up.

Results

The median time of overall survival was 10.33 months (range 5.3–16.6 months) and the median of progression-free survival was 6.8 months (3.03–14 months). The median values with minimum and maximum ranges for NLR, PLR, and LMR were 2.56 (0.92–15.63), 140.35 (75.47–661), and 3.2 (0.7–9.6), respectively. There was a statistically significant correlation between NLR and OS ($r = –0.320$, $p < 0.05$) NLR and PFS ($r= –0.452$, $p < 0.05$) and LMR and OS ($r = 0.312$, $p < 0.05$). The results are presented in table I. In the case of NLR, we have performed the log rank test for an NLR cut-off value of 3. The results are presented in table II. The likelihood of survival in patient groups based on the NLR result is presented in figure 1. There was no statistically significant correlation in BMI and PFS ($r = 0.197$, $p = 0.222$), or BMI and OS ($r = 0.185$, $p = 0.267$). In terms of PLR (cut off

Table I. Spearman's rank correlation coefficient

Tested quantitative data	R coefficient
NLR and PFS	–0.320 ($p < 0.05$)
NRL and OS	–0.452 ($p < 0.05$)
PLR and PFS	–0.177 ($p = 0.245$)
PLR and OS	–0.296 ($p = 0.054$)
LMR and PFS	0.219 ($p = 0.148$)
LMR and OS	0.312 ($p = 0.052$)

NLR – neutrophil-lymphocyte ratio; PFS – progression-free survival; OS – overall survival

Table II. Log-rank test results for groups based on NLR result

	Median in NLR < 3 group (months)	Median in NLR ≥ 3 group (months)	Log-rank test results
PFS	8.46 (3.67–14.5)	4.11 (2.4–9.97)	$p = 0.0587$
OS	14.5 (8.7–17.87)	5.78 (4.53–11.33)	$p < 0.05$

PFS – progression-free survival; OS – overall survival

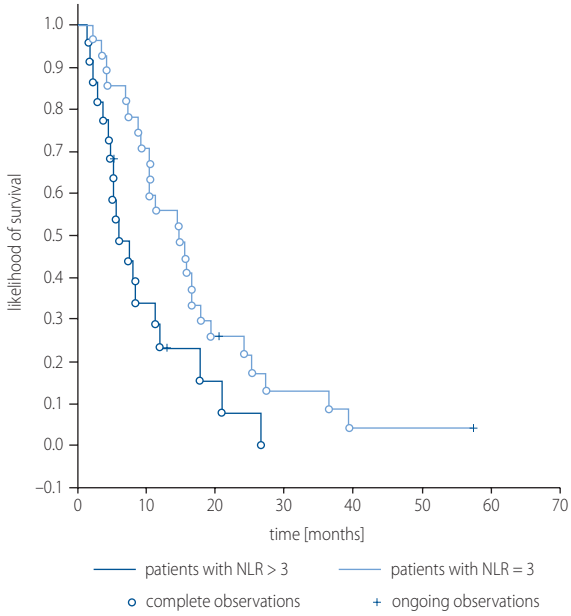

Figure 1. The Kaplan–Meier estimator of survival in patient groups based on NLR result

value 150) and LMR (cut off value 3), we have not determined statistically significant differences in PFS or OS (tab. III, IV).

Discussion

The growth of solid tumors is related to inflammation of surrounding tissues, affecting every stage of oncogenesis. On the other hand, the growth of a tumor increases the local inflammation, causing the self-escalating process of tumor progression [12]. An increasing inflammation state leads to chemotaxis of immunologic cells such as neutrophils, macrophages, dendritic cells, lymphocytes, and mastocytes, which through expression of various cytokines determine the local immunologic response and affect tumor growth. The dominance of pro-inflammatory cytokines lead to the collapse of a systemic immunological response [13]. Granulocytes, as a part of immunological response affect oncogenesis on many levels. The release of reactive oxygen and nitrogen forms by neutrophils cause local damage of epithelium, what stimulates prostaglandin E2 synthesis directly affecting oncogenesis [14, 15]. What is more, those cells produce neutrophilic elastase, which increases tumor cell proliferation [16]. Granulocytes can also decrease the immunological response of CD8 lymphocytes through nitrate oxygen synthase and TGF beta production [17]. Morphological evidence of local activity of immunological cells is the neutrophil-to-lymphocyte ratio.

In recent years, a few studies have determined the role of NLR as a prognostic factor in patients with PDAC in different clinical stages of disease [18–20]. In this study, NLR levels were evaluated in patients beginning systemic treatment with the FOLFIRINOX regimen due to metastatic PDAC. Values of NLR above 3 were associated with shorter median of overall survival. For NLR above 3, PFS and OS medians were 4.1 and 5.8 months, respectively. In the group of patients with an NLR lower than 3, the medians were 8.5 month and 14.5 months. These results are in accordance with previous studies. In the M. Piciucchi study in patients with metastatic PDCA, the values of NLR above 5 were associated with shorter OS, compared to patients with NLR below 5 (3 months *vs.* 7 months, $p < 0.003$) [21].

In the M. Shusterman study, NLT turned out to an independent prognostic factor in advanced PDAC. The median time of OS was 7.4 months for patients with NLR above 5, compared to patients with NLR below 5 (range of OS from 5 to 20 months) [22]. A study by S. Cetin presents greater differences between groups with NLR above 3.54 and below 3.54. For those cut-off values, median OS times were 9 months and 17 months respectively [23]. The presented results are also compatible with meta-analyses, proving that increased NLR was associated with poor prognosis in metastatic PDAC [24, 25].

In the case of LMR and PLR, we did not observe such results. This is contradictory to observations of meta-analyses proving that LMR and PLR might be independent prognostic factors [26–30]. The most probable reason for such discrepancy is the relatively small number of patients in the present study, together with the relative weak impact of LMR and PLR on the prognosis shown in the meta-analyses. LMR and PLR are parameters that

Table III. Log-rank test results for groups based on PLR result

	Median in PLR < 150 group (months)	Median in PLR ≥ 150 group (months)	Log-rank test results
PFS	8.15 (3.03–14.0)	4.76 (3.0–14.03)	p = 0.8565
OS	11.36 (6.03–17.87)	7.68 (4.53–11.93)	p = 0.6746

PFS – progression-free survival; OS – overall survival

Table IV. Log-rank test results for groups based on LMR result

	Median in LMR < 3 group (months)	Median in LMR ≥ 3 group (months)	Log-rank test results
PFS	5.50 (3.7–10.33)	8.25 (2.8–14.03)	p = 0.2461
OS	8.3 (4.76–16.5)	10.85 (6.28–17.23)	p = 0.4469

PFS – progression-free survival; OS – overall survival

require further analysis in patients with metastatic PDAC during systemic therapy.

Our study is one of the few studies that have proved the utility of NLR for a selected group of patients with metastatic PDAC during first line systemic therapy with FOLFIRINOX regimen.

Conclusions

This study proves the prognostic value of NLR in patients with PDAC in IV clinical stage treated with FOLFIRINOX chemotherapy.

Conflict of interest: non declared

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