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Very high and very low levels of preoperative absolute monocyte count indicate poor long-term survival outcomes in patients with pancreatic adenocarcinoma. A preliminary study

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Introduction. We aimed to assess the prognostic significance of preoperative absolute monocyte count (AMC) in baseline peripheral blood samples among pancreatic cancer (PC) patients as possible manifest signs of non-optimal immunity status.

Material and methods. PC patients who underwent palliative surgical treatment without earlier chemo- or radio--therapy (n = 59).

Results. Median AMC was comparable in each subgroup, showing no significant differences. We have adopted an arbitrary trichotomic AMC division: low (<0.4 G/l, n = 9), medium (>0.4 and ≤0.6 G/l, n = 36) and high (>0.6 G/l, n = 14). Optimal (medium AMC) and non-optimal (both low and high AMC) was independent and a statistically significant predictor of OS. Resectability and optimal AMC constituted best Cox proportional hazard model, being equivalent predictors of OS.

Conclusions. Baseline AMC status may be an independent predictor of OS in this group of patients. Further research is needed to explain the biological nature of this phenomenon more widely.

Key words: pancreatic cancer, immune system, monocytes, lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR)

Introduction

Pancreatic cancer (PC) is one of the most malignant cancers, with the 5-year survival rate approaching 9% [1]. Late onset of symptoms, difficulties in pre-surgical diagnosis confirmation and low chemosensitivity justify the notoriety of PC [2]. Little is known about the exact role of the immune response in driving the poor prognosis of PC, apart from the fact that it is considered relatively low immunogenic [3]. The prognostic value of pretreatment AMC as well as the lymphocyte-to-monocyte ratio were studied in PC without an unequivocal conclusion. Some cancers can secrete GM-CSF and G-CSF, influencing directly the white blood cell counts, but this phenomenon has not been explored in cases of PC [4]. High pretreatment absolute monocyte count (AMC) generally drives poor prognosis factors in many cancers, including PC [5]. There is significant evidence that monocytes may influence the course of PC, but

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their role cannot be easily translated into simple hypothesis linking them to pancreatic cancer. In terms of quantity, AMC represents the state of the whole organism's monocyte-associated immune forces, associated with the course of neoplastic disease with numerous bonds. Therefore, we hypothesize that both relatively low and high pretreatment AMC could be linked to a poorer course of PC, as it generally reflects the non-optimal immunity status of the patient.

Material and methods

We retrospectively collected data of consecutive PC patients with disease preoperatively qualified as resectable, who underwent surgical treatment in the General and Transplant Surgery Department between the years 2013–2016 without earlier chemo- or radio-therapy. Additional inclusion criterium was having PC confirmed in postoperative material (n = 59). We analysed their sex, age, preoperative AMC (from routine venous blood tests taken one day prior to surgery, after admission), tumour location (head/body-tail), type of performance (resection/non resectable) and overall survival (OS). Laboratory norm for AMC was $<0.8 \times 10^9$/l. The study was approved by the local Ethical Committee.

Statistical analysis was conducted using Statistica 13 PL. We used the Kaplan-Meier method to estimate survival functions and the log-rank test to compare survival curves. To describe the size of effect we used hazard ratios (HR) from proportional hazard Cox regression models both for uni- and multivariate analysis.

Table I. Tested parameters in the study group – basic characteristics

Features	Number of patients (%)	AMC median, range
age:		
≥60	21 (35.6%)	0.58 (0.20–1.07)
<60	38 (64.4%)	0.56 (0.29–1.00)
sex:		
male	29 (49.2%)	0.60 (0.29–1.07)
female	30 (50.8%)	0.50 (0.20–0.80)
location:		
head	39 (66.1%)	0.52 (0.20–1.07)
body-tail	20 (33.9%)	0.57 (0.50–0.60)
resectability:		
resection	33 (56.0%)	0.54 (0.20–0.90)
non-resectable	26 (44.0%)	0.60 (0.21–1.07)
AMC:		
<0.4 (low)	9 (15.3%)	–
0.4–0.6 (optimum)	36 (61.0%)	–
>0.6 (high)	14 (23.7%)	–

Results

Table I contains detailed study group characteristics. Median AMC was comparable in each subgroup, showing no significant differences. According to our hypothesis, we searched optimal cut-off values using the visual method (based on the OS *vs.* AMC chart, fig. 1). We have adopted an arbitrary trichotomic division:

- low (<0.4 G/l, n = 9) AMC,
- medium (>0.4 and ≤0.6 G/l, n = 36) AMC,
- high (>0.6 G/l, n = 14) AMC.

Low AMC corresponded to a high percentage of resection – 77.8%, (respectively: medium MC – 55.3%, high MC – 35.7%). There was no statistically significant correlation between AMC and age (r = 0.0013, p = 0.992), as well as between the AMC subgroup and resectability (p = 0.12).

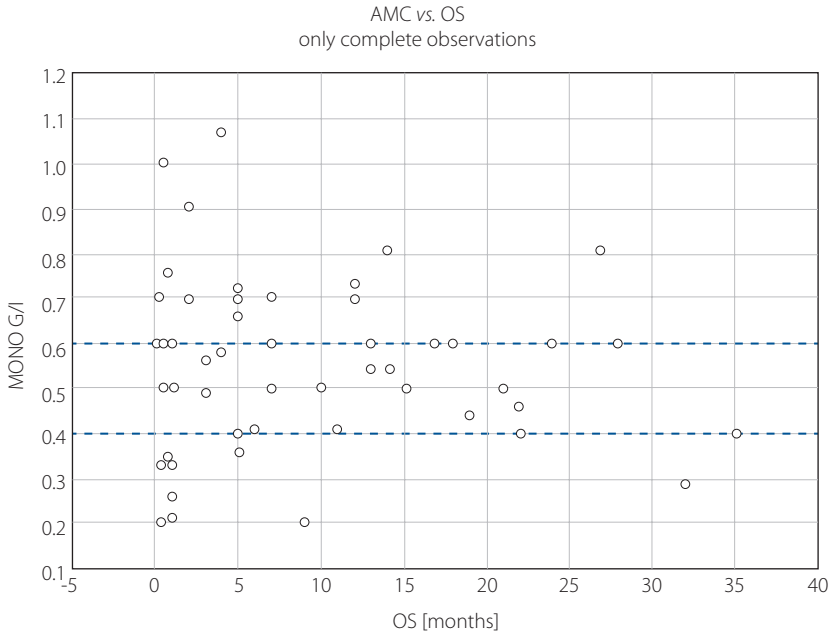

Figure 1. AMC distribution among all patients. Dotted lines corresponds with the cut-off points adapter

Table II. Characteristics of the study subgroups in the context of tested parameters and AMC levels

Parameter (n; %)	Low AMC	Medium AMC	High AMC
sex:			
male	4 (44.4%)	15 (41.7%)	10 (71.4%)
female	5 (55.6%)	21 (58.3%)	4 (28.6%)
age:			
≥60	6 (66.7%)	24 (66.7%)	8 (57.1%)
<60	3 (33.3%)	12 (33.3%)	6 (42.9%)
resectablity:			
resection	7 (77.8%)	21 (58.3%)	5 (35.7%)
non-resectable	2 (22.2%)	15 (41.7%)	9 (64.3%)
6-months survival:			
yes	2 (22.2%)	24 (66.7%)	5 (35.7%)
no	7 (77.8%)	12 (33.4%)	9 (64.3%)
12-months survival:			
yes	1 (11.1%)	20 (55.6%)	2 (14.3%)
no	8 (88.9%)	16 (44.4%)	12 (85.7%)

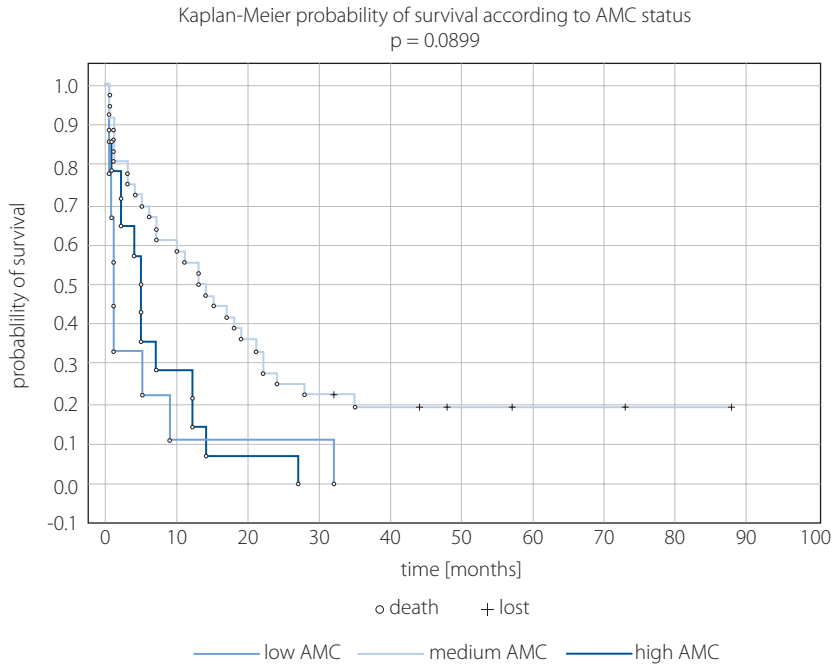

Figure 2. Survival curves for pancreatic cancer patients of low, medium and high AMC. Log-rank p = 0.0899

Survival analysis

The median survival time for low, medium and high AMC was respectively: 1; 13.5; 5 months (p = 0.0899; tab. II, fig. 2). AMC divided in this way was not a significant predictor of OS, but redefined into optimal (medium AMC) and non-optimal (both low and high AMC) statistically significant determinants of OS (p = 0.009) and an independent predictor of OS. Resectability and optimal AMC constituted the best Cox proportional hazard model, being equivalent predictors of OS (tab. III, fig. 3).

Discussion

We postulate two main causes for observed low AMC phenomenon in our study group: a specific, but of little quantitative effect – the process of monocytes migration to the tumour tissue and a non-specific, but responsible for a major part of this symptom, decrease of monocytes production.

A low monocyte count may be both isolated monocytopenia as well as other forms of leukopenia. Leukopenia, which is a secondary immunodeficiency state, may develop in some cases of malnutrition [6]. A white blood cell count below the normal range was found in 39.7% of anorexia nervosa patients [7] and in 62% of hunger-strike patients [8]. 85% of PC patients experience a reduction in their body weight [9]. Immune system stimulation lead to raising the AMC. High AMC patients tend to be younger than others, suggesting that personal maximum is a function of the organism's ava-

Table III. Cox proportional hazard regression – univariates and the best multivariate model

Parameter (n; %)	HR (range)	p
	univariate	
sex	0.99 (0.58–1.72)	0.984
age ≥60	0.76 (0.43–1.33)	0.343
resectablity	0.37 (0.21–0.67)	0.0009
low, medium, high AMC	1.07 (0,62–1.87)	0.786
optimal AMC	0.39 (0.22–0.70)	0.001
	multivariate	0.00002
resectablity	0.34 (0.18–0.62)	0.0005
optimal AMC	0.36 (0.20–0.65)	0.0007

ilable resources [10]. The phenomenon of GM-CSF secreting tumours also could be responsible for the special prognostic role of high monocyte count in patients with PC, but this is not in line with our results, as the secretion of GM-CSF was linked with an antiangiogenic and antitumour effect, resulting in lower mortality; as it has been not investigated in PC yet, this option remains only a theoretical possibility [4].

Absolute monocyte count was reported to be a predictor of outcome, dichotomizing patients into groups with a good and bad prognosis. As the rationale comes from AMC translation into the general anticancer immunity state, in our opinion it is justified to read them in context with each other, independently from the studied malignancy type. Until now there was only one study discussing this issue in PC patients (cut-off 0.6, p = 0.23) [5]. The approach of other authors was either dichotomic, or trichotomic, depending on the number of the prognostic group. The trichotomic approach assumes an optimal AMC group with good prognosis and extrema (low and high AMC) of bad prognosis groups. Bruckner et al. described it for the first time in patients with gastric cancer in JAMA (1982) [11]. In 2013 Herishanu et al. postulated on it in his work on chronic lymphocytic leukemia [10]. Our study hypothesis, results and conclusions come in line with their papers (cut-offs respectively: 300 and 900; 250 and 750 – the exact cut-offs are different, probably because of the study group size and specific features, but their middle value stays similar). Other authors proposed following single cut-off values: for myeloproliferative diseases: 630, 700, 800, 1000, 1500 and for solid tumours: 300, 408, 700, 800, 900 [12–19]. Although the statistical significance in the Kaplan-Meier survival analysis was generally reached, these results cannot be considered reproducible. A possible explanation is the skewness of AMC distribution (asymmetrical distribution of low and high AMC patients) in the studied group and considering only one cut-off point idea. Schmidt et al. did not include patients with AMC below the norm into his malignant melanoma study, which constitutes a bridge between the dichotomic and trichotomic approach, as well as can be the result of search for statistical significance when it is impossible to reach with single cut-off point with those patients included [20].

LMR prognostic ratio context

The pretreatment lymphocyte-to-monocyte ratio was a widely tested prognostic factor in many types of cancer, including pancreatic cancer. Their general idea of a bad prognosis blood phenotype can be presented as following:

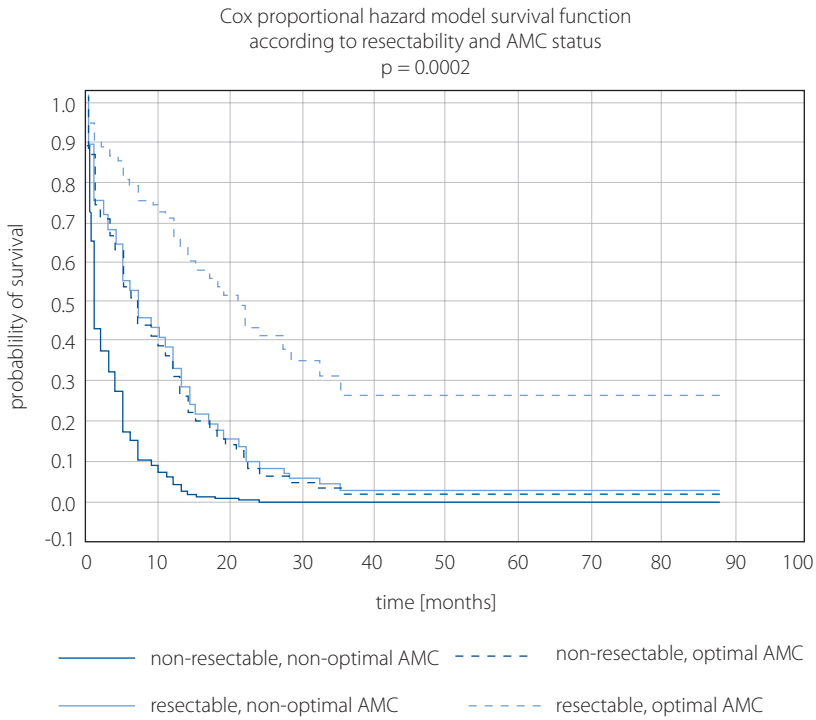

Figure 3. Chart illustrating Cox proportional hazard model survival function according to resectability and AMC status

$$\frac{lymhocyte\ count}{monocyte\ count} > k$$

$$lymhocyte\ count > k \times monocyte\ count$$

Where k is the cut-off point set for the particular study group, so it is kind of an unfavourable balance between white blood cell type counts in peripheral blood. The results are partially repeatable (with relatively similar HR 0.34–0.78 but with a wide range of proposed cut-off points 2.05–4.62) [21–28].

Laboratory norms for monocyte ($<0.8 \times 10^9$/l) and lymphocyte ($1.0–4.5 \times 10^9$/l) counts suggest that a healthy adult organism has a few times more lymphocytes than monocytes in their peripheral blood. The way of thinking laying under the LMR idea raises several doubts. First, any complete theory or hypothesis explaining the reason of observed phenomenon was presented since now, even though the outcome of many studies seems still statistically significant. Secondly, the LMR idea omits the problem of patients with very low white blood cell counts, which as a form of immunodeficiency has obviously undeniably bad prognosis. Thirdly, it puts over the cut-off points great deal of the norm. In light of this study's results, bad prognosis of high LMR values can just speak for blood morphology phenotypes of good prognosis existence, that are not describable using simple linear functions. It is possible that their nature is not about the mutual relationship of different white blood cell types, but about their raw, effective count and even more importantly, their function. A better understanding of the immune system's importance for pancreatic cancer patients will probably lead to finding new, precise biomarkers to better personalize treatment [29–30].

Limitations of the study

Although the study group size was enough to find our hypothesis statistically significant, it still can underestimate some nuances, for example, the exact comparison of low *vs.* high AMC. We also did not analyse the data about chemo- or radio--therapy regimens used postoperatively, so we cannot exclude that the study is biased by some treatment-related factors. As we did not collect the exact TNM, grade, comorbidity or BMI, our results cannot be assessed in this context yet.

Conclusions

We are the first to describe the association between preoperative non-optimal AMC and the course of the disease in pancreatic adenocarcinoma patients. As the monocyte count seems at least a potential predictor of OS, the need for further research in this field is crucial. We postulate on not only the existence of good prognosis blood morphology profile, but also search for a universal marker of the current state of immune system--cancer interaction.

Conflict of interest: none declared

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