Neutrophil/lymphocyte ratio helps select metastatic pancreatic cancer patients benefitting from oxaliplatin

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Abstract.

BACKGROUND: High Neutrophil/Lymphocyte ratio (NLR), as a measure of enhanced inflammatory response, has been negatively associated with prognosis in patients with localized pancreatic ductal adenocarcinoma (PDA).

OBJECTIVE: In the present study, we aimed at investigating the prognostic value of NLR in two homogeneous groups of chemotherapy-naïve metastatic PDA patients. Patients were treated with either gemcitabine (GEM) or gemcitabine/oxaliplatin (GEMOXA). We also assessed whether NLR could identify patients benefiting from the use of oxaliplatin.

METHODS: Consecutive PDA patients treated at the Medical Oncology Unit of Tor Vergata University Hospital of Rome with either GEM or GEMOXA were included ($n = 103$). NLR was assessed before and during chemotherapy and correlated with outcome together with common clinical and biochemical variables.

RESULTS: Among 17 analyzed variables NLR, Karhofsky Perfomance Status (KPS), d-dimer and erythrocyte sedimentation rate were found to be significantly associated with median Overall Survival (mOS) at the univariate analysis. Only NLR and KPS were independent prognosticator at multivariate analysis, with NLR displaying the highest statistical significance. NLR was also predictive of oxaliplatin activity, as only patients with NLR > 2.5 (cutoff determined upon ROC analysis) derived benefit from GEMOXA over GEM.

CONCLUSIONS: NLR is both an independent prognostic and predictive factor in metastatic PDA, since only patients with high NLR seem to benefit from the addition of oxaliplatin. NLR may help select patients for whom a particularly poor prognosis might justify more intensive, yet less tolerable, combination regimens.

Keywords: Neutrophil/lymphocyte ratio, pancreatic ductal adenocarcinoma, gemcitabine, oxaliplatin

1. Introduction

Pancreatic ductal adenocarcinoma (PDA) is one of the most aggressive tumors, with dismal prognosis.

At the time of diagnosis, most patients present with inoperable disease and have a median survival of 6 to 8 months [1].

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For unresectable patients, systemic chemotherapy is the standard. Until recently, guidelines have recommended gemcitabine (GEM) as the standard first-line treatment, because of its efficacy and its manageable toxicity also in frail subjects [2]. Up to 2011, polychemotherapy regimens could not demonstrate a major advantage in survival over gemcitabine monotherapy, even in large randomized phase III trials and, therefore, were not used as a standard [3–12].

However, a meta-analysis published in 2007 found a small but significant benefit from the addition of platinum compounds or fluorouracil to gemcitabine [13], and in some centers GEM-based combinations (e.g. gemcitabine + oxaliplatin (GEMOXA), gemcitabine + cisplatin, gemcitabine + fluoropyrimidines, gemcitabine+erlotinib) have been considered as a possible choice for patients with good performance status (PS) and the need for a rapid radiological response [2,13].

In 2011, results from the PRODIGE 4/ACCORD 11 trial were published demonstrating for the first time that the three-drug FOLFIRINOX regimen was superior to GEM alone for patients with excellent PS [14].

Lately, the addition of an albumin-bound taxane to gemcitabine was found to produce a 28% reduction in the risk of death in the MPACT trial [15].

Considering all these findings, GEM alone may be a suboptimal treatment for particularly fit patients. It would be desirable to identify specific pre-treatment prognostic factors able to determine which subgroup of patients would really benefit from more aggressive combination chemotherapy.

Systemic inflammation is a process associated with a number of pathological conditions, such as metabolic disorders [16], atherosclerosis [17], osteoporosis [18] and cancer [19–23]. It might be considered as a double-edged weapon in that it represents the first line immune defense but also a source of cytokines and growth factors with potentially adverse effects.

Blood neutrophil to lymphocyte ratio (NLR) is a reliable biomarker of systemic inflammatory response. High NLR has been found to have an adverse effect on prognosis for localized pancreatic and periampullary malignancies. A few studies have recently confirmed these results also in the metastatic setting [24].

Owing to the worse reported outcome, PDA patients with high NLR are ideal candidates for more aggressive treatment with gemcitabine-based combination chemotherapy. In an update of the MPACT study, the effect of NLR was investigated, and there appeared to be a higher efficacy of nab-paclitaxel plus gemcitabine regimen in patients with NLR > 5 [15].

Up to 2011, in our center GEMOXA has been the preferred option for PDA patients with good performance status, because of the convenient schedule (biweekly administration) and the relatively good tolerance

Authors acknowledge that the preference for GEMOXA can be questionable; however results in the present study are hypothesis generating and could be taken into consideration for future studies aiming at identifying predictive markers for other combination regimens.

None of the previous researches have investigated whether NLR is predictive in discriminating patients who would benefit from the GEMOXA doublet over GEM alone.

The aim of the present study was to select two homogenous groups of patients, receiving either GEMOXA or GEM, depending on reasons other than performance status or general health condition. Main reasons of regimen choice were patient preference or pre-existent neuropathy (mainly diabetes-related) indicating oxaliplatin withdrawal. The prognostic and predictive role of NLR was investigated.

2. Materials and methods

Among all consecutive patients referred to the Medical Oncology Unit of Tor Vergata University Hospital, patients with histologically confirmed diagnosis of PDA and measurable metastatic disease were eligible for this retrospective observational study. The evaluated referral period was between April 2008 and October 2011. Patients with active infection, autoimmune disease and stable treatment with steroids, were excluded.

Included patients were required to be chemotherapy-naïve. Patients had to have Karnofsky PS (KPS) 100 to 80 and adequate hematological (Hb $\geqslant$ 9 g/dl, white blood cell (WBC) $\geqslant$ 2000/mm^3, platelet count $\geqslant$ 60000/mm^3), hepatic (bilirubin $\leqslant$ 1.5 $\times$ upper limit of normal (ULN), alanine amino-transferase (ALT) and aspartate aminotransferase (AST) $\leqslant$ 1.5 $\times$ ULN), and renal (creatinine $\leqslant$ 1.5 $\times$ ULN) functions. Patients with poor performance status (KPS < 80) were excluded from the study.

A standard first-line therapy with either GEM (gemcitabine 1000 mg/m^2 weekly, 7 weeks on 1 week off for the first cycle, 3 weeks on 1 week off for the following cycles) or GEMOXA (gemcitabine 1000 mg/m^2 day 1, oxaliplatin 100 mg/m^2 day 1, cycles repeated every 2 weeks) was chosen for treatment.

As per internal guidelines, the preferred regimen for patients with KPS > 80 was GEMOXA.

However, in some cases the GEM regimen was adopted, with main reasons for withdrawing oxaliplatin being 1) patient's preference (i.e. patients not willing to receive a more toxic regimen in light of a possible minimal improvement in disease outcome) or 2) pre-existent peripheral neuropathy (mainly diabetes-related).

Treatment was continued until tumor progression, unacceptable toxicity, or request of termination by individual patients.

Assessment of response was performed every 8 weeks of treatment by comparison of a thorax/abdomen/pelvis CT scan, according to RECIST criteria, with the baseline CT scan that had been performed within 45 days prior to chemotherapy initiation.

As per routine practice, the following data were collected in the institutional electronic medical records before treatment commencement: gender, age, body mass index (BMI), KPS, circulating tumor markers (carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA 19.9)), routine hematology including full blood count (neutrophils, lymphocytes, monocytes, haemoglobin and platelets), biochemical blood tests including Alkaline Phosphatase (ALP), Albuminemia, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH). KPS evaluation, BMI, CEA, CA 19.9, routine hematology and biochemical blood tests were also performed during treatment at each chemotherapy administration (i.e. every week/two weeks). Hematology test allowed NLR calculation. Baseline data were considered evaluable if collected within 3 weeks before the start of the treatment.

All patients signed an informed consent to data analysis for retrospective studies.

Patients out of treatment, in palliative care, but still capable of attending the clinic, were offered to be clinically followed-up every two months at the Medical Oncology Unit Outpatient Service of Tor Vergata University Hospital.

The study was approved by the local ethics committee and Institutional Review Board and therefore carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.1. Statistical analysis

The primary endpoint was to evaluate the predictive value of baseline and one-month NLR for Overall Survival (OS), defined as time from treatment start to death from any cause. If a patient had not died, OS was censored at the time of the last follow-up.

The secondary endpoint was the association between NLR and: (1) progression-free survival (PFS), defined as the period beginning on the date of treatment commencement and ending with the first observation of disease progression or death from any cause, if a patient had not reached the progression endpoint, PFS was censored at the time of the last follow-up; (2) overall RECIST-defined radiological response rate (ORR) divided into two main categories: presence (complete + partial responses) or absence (stable + disease progression) of radiological tumor response.

Another secondary endpoint was the association between known prognostic factors in PDA and OS.

Examples of prognostic factors for PDA are the tumor marker CA19.9, which is proportional to the tumor burden [25], ALP, which is both an inflammatory and cholestasis marker [26], and d-dimer, which is associated with an enhanced coagulative cascade [27].

Associations between prognostic variables and PFS or OS were examined using the Kaplan–Meier method with long rank test and Cox-regression analysis to assess for differences between subgroups and estimation of hazard ratio (HR) and its associated 95% confidence interval (95% CI).

A Cox proportional hazards regression analysis was performed to evaluate the association between selected prognostic factors and the primary endpoint (OS) in multivariable models.

In the multivariate Cox-regression analysis, the enter method was used to enter independent variables into the model (i.e., all variables were entered into the model in one single step without checking for significance). Only variables found significant (i.e. p value < 0.05) at the univariate analysis were included in the multivariate model.

Associations between dichotomized prognostic factors and ORR were evaluated by the chi-square test.

A Receiver Operating Curve (ROC) was constructed to set the most discriminatory NLR cut-off, using long vs short-term survival (i.e. > vs < 6 months) as a classification variable. The choice of using the 6 months value was based on convenience since only three patients among those still alive had a follow-up inferior to 6 months, and a relevant proportion of patients (38%) were classified as short-term survivors.

Differences in patient characteristics between NLR subgroups were tested using either chi-square or T test.

All statistical tests were two-sided. Analyses were done using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

Table 1
Characteristics of the 103 study patients. Values refer to absolute number (n.) of patients except when otherwise specified. KPS: Karnofsky performance status, GEM: gemcitabine, GEMOXA: gemcitabine+oxaliplatin, WBC: white blood cells, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), body mass index (BMI), Hb: haemoglobin, NLR: neutrophil-lymphocyte ratio

Characteristic	Category	n. of patients
Clinical		
Sex	Male	53
	Female	50
Age	Median	67 years
	Range	41–84 years
KPS	100	53
	90	35
	80	15
Type of chemotherapy	GEM	46
	GEMOXA	57
Diabetes at diagnosis	Yes	25
	No	78
Biochemical		
LDH	Median	305 U/l
	Range	122–1162 U/l
ALP	Median	168 U/l
	Range	37-2427 U/l
d-dimer	Median	340 ng/mL
	Range	55–13615 ng/mL
CRP	Median	19.00 U/l
	Range	0.01–252.60 U/l
ESR	Median	30 mm/h
	Range	18–120 mm/h
Albumin	Median	3.5 g/dL
	Range	2.0–4.8 g/dL
CA 19-9	Median	400 U/ml
	Range	1–100000 U/ml
CEA	Median	3 ng/ml
	Range	0.3–531.7 ng/ml
WBC	Median	$7.1*10^3/mm^3$
	Range	$2.1–25.4*10^3/mm^3$
Neutrophils	Median	$4.4*10^3/mm^3$
	Range	$0.5–20.7*10^3/mm^3$
Lymphocytes	Median	$1.7*10^3/mm^3$
	Range	$0.3–5.3*10^3/mm^3$
NLR	Median	$2.5 \ mm^3/mm^3$
	Range	$0.3–22.8 \ mm^3/mm^3$
Monocytes	Median	$0.5*10^3/mm^3$
	Range	$0.03–2.69*10^3/mm^3$
Hb	Median	12.3 g/dL
	Range	9.4–16.0 g/dL
Platelets	Median	$240*10^3/mm^3$
	Range	$63–590*10^3/mm^3$
BMI	Median	$23 \ kg/m^2$
	Range	$16–38 \ kg/m^2$

3. Results

3.1. Patients' characteristics and treatment delivery

Among 203 consecutive patients referred to our Unit between April 2008 and October 2011, 103 patients, 50 female and 53 male, were included into the study (Table 1).

All included patients were treated with either GEM (N = 46) or GEMOXA (N = 57) as per protocol for at least two cycles. The median age at baseline was 67 years (range, 41–84). There was no imbalance in KPS between GEM and GEMOXA group (KPS 80 or 90 in 53% and 42% of patients, respectively, chi-square p value = 0.209). Median BMI at treatment start was 23 (range 16–34).

Routine biochemical tests, some of which are well recognized prognostic factors, were performed, as per routine practice, at baseline (Table 1) and at each chemotherapy administration. Adverse biochemical features of ALP > ULN (i.e. 129 U/L), CA19.9 > ULN (i.e. 37 U/mL), CEA > ULN (i.e. 5 ng/mL), were observed in 65%, 80% and 32% of cases, respectively.

Median NLR was 2.518, with 25 patients having NLR > 5. The majority of patients (54%) had hematology and biochemical tests the day of chemotherapy commencement, just before drug administration, or the day before; only seven patients had blood tests more than ten days prior to the start of treatment.

Detailed demographic and clinical features are summarized in Table 1.

3.2. GEM vs GEMOXA

Among the 103 patients selected for the study, median number of treatment cycles administered was 3 (range, 2–12) and 6 (range, 3–13), in the GEM and GEMOXA group, respectively. In the whole population, ORR was 14%, with a disease control rate (DCR, response + stable disease at 3 months) of 38%.

As of May 2013, 93 out of 103 patients had reached the progression endpoint. median PFS was 4 months (95% CI 3.4–5.5). Eighty-eight patients had died and 15 were alive. Median follow-up of surviving patients was 22 months (range 2–51). Median OS was 7 months (95% CI 6.1–8.2).

In the whole study cohort, GEMOXA displayed a superior OS as compared to GEM, with an mOS of 8.0 and 5.8 months, respectively, Hazard Ratio, HR 1.46 (95% CI 0.94–2.25), but this was of borderline statistical significance (p 0.07, Fig. 1).

3.3. Prognostic value of NLR

To investigate the prognostic and predictive value of NLR in study patients, a ROC analysis was performed to set the NLR cutoff with the most favourable
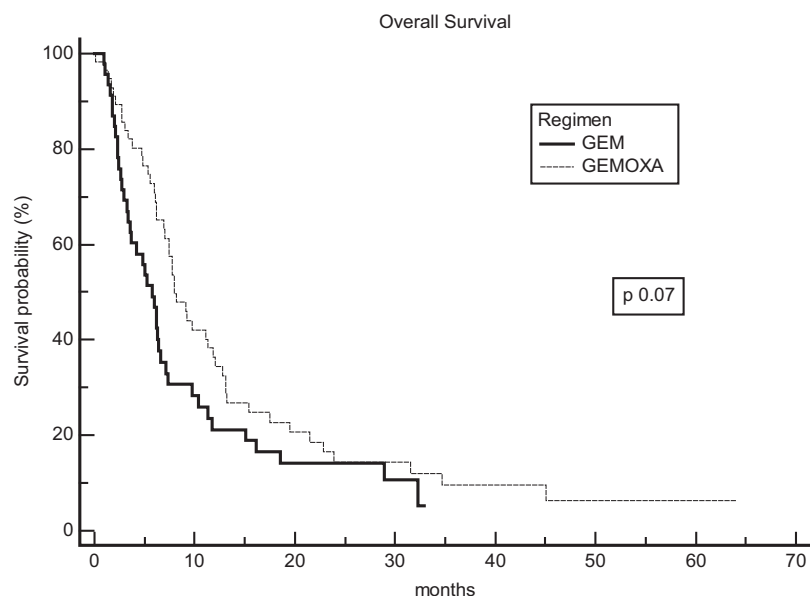
Overall Survival

Fig. 1. Overall Survival and first-line chemotherapy regimen in 103 analysed patients. GEM: gemcitabine monotherapy. GEMOXA; gemcitabine plus oxaliplatin.
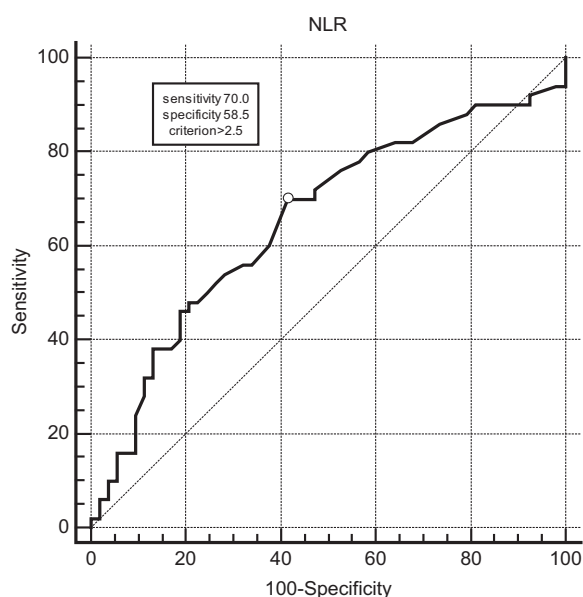
NLR

Fig. 2. Receiver Operating Curve (ROC) analysis to set best neutrophil-lymphocyte ratio (NLR) cutoff.

specificity and sensitivity (Fig. 2). Overall survival was used as the classification variable by categorizing patients as long (more than 6 months) and short-term ($<$ 6 months) survivors. The value of 2.5 (< 2.5 vs > 2.5) was found to be the ideal cutoff to distinguish short vs long survivors with 70% sensitivity and 58.5% specificity.

Using the cutoff value derived from ROC analysis, NLR was confirmed to be a biomarker significantly associated with overall survival in the whole study cohort, with mOS of 9.2 and 6.0 months for patients with NLR $<$ vs $>$ 2.5, respectively, HR 1.95 (95%CI 1.28–2.97), p 0.001. The prognostic power of NLR was also demonstrated with regard to PFS: mPFS 6.4 and 3.4 months, respectively, HR 2.39 (95%CI 1.57–3.62), $p < 0.0001$.

As compared to low NLR patients, high NLR patients had higher baseline d-dimer (mean 1228 vs 383 ng/mL, p 0.01), monocytes (mean 0.75 vs $0.53 * 10^3/mm^3$, p 0.02) and ESR (mean 38 vs 30 mm/h, p 0.03). No other significant differences were detected (in particular no difference in diabetes incidence between high vs low NLR) [28].

3.4. NLR and other prognostic factors

To evaluate NLR in conjunction with other clinical and biochemical variables potentially influencing prognosis, univariate and multivariate Cox-regression analyses for the primary endpoint OS were performed (Table 2). At univariate analysis, NLR taken as a continuous variable was confirmed to be significantly associated with survival, with a 13% increased risk of death per 1-unit increase in NLR = exp(b) 1.13, 95% CI 1.06–1.20, p 0.0001. D-dimer (continuous variable), ESR (continuous variable) and KPS (80 or 90 vs

Table 2
Univariate and Multivariate Cox-regression analysis for Overall Survival. Only variables with $p < 0.05$ at univariate analysis were run in the multivariate model. KPS: Karnofsky performance status, GEM: gemcitabine, GEMOXA: gemcitabine + oxaliplatin, WBC: white blood cells, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), body mass index (BMI), Hb: haemoglobin, NLR: neutrophil/lymphocyte ratio, b: cox-regression coefficient of the relevant variable, SE: standard error for b, Wald: Wald statistic result to derive p-value, Exp: exponential, CI: Confidence Interval. Variables are taken as continuous unless otherwise specified (i.e. x-value vs y-value shape). Exp(b) represents the Hazard Ratio (HR). For continuous variables, HR refers to the hazard of death for each 1-unit increase of the variable itself

Covariate	B	SE	Wald	Exp(b)	95% CI of Exp(b)	P-value
Univariate						
NLR	0.1198	0.0303	15.6696	*1.1272*	1.0627 to 1.1958	*0.0001*
d-dimer	0.0002	0.0001	9.8298	*1.0002*	1.0001 to 1.0003	*0.0017*
KPS (80–90 vs 100)	0.6143	0.2243	7.5043	*1.8484*	1.1937 to 2.8623	*0.0062*
ESR	0.0160	0.0068	5.5764	*1.0161*	1.0028 to 1.0296	*0.0182*
GEM vs GEMOXA	0.3857	0.2173	3.1510	*1.4706*	0.9627 to 2.2463	*0.0759*
Sex (female vs male)	0.3845	0.2167	3.1491	*1.4689*	0.9627 to 2.2413	*0.0761*
ALP	0.0005	0.0004	1.4542	*1.0005*	0.9997 to 1.0014	*0.2279*
BMI	−0.0332	0.0295	1.2697	*0.9673*	0.9133 to 1.0246	*0.2598*
Albumin	−0.2108	0.1894	1.2394	*0.8099*	0.5599 to 1.1717	*0.2656*
Monocytes	−0.2089	0.2429	0.7399	*0.8114*	0.5053 to 1.3031	*0.3897*
Platelets	−0.0009	0.0010	0.7313	*0.9991*	0.9971 to 1.0011	*0.3925*
CA 19-9	0.0000	0.0000	0.6821	*1.0000*	1.0000 to 1.0000	*0.4089*
Hb	−0.0635	0.0877	0.5240	*0.9385*	0.7910 to 1.1135	*0.4692*
Diabetes (yes vs no)	0.1047	0.2473	0.1794	*1.1104*	0.6856 to 1.7985	*0.6719*
CEA	−0.0006	0.0015	0.1377	*0.9994*	0.9964 to 1.0024	*0.7106*
CRP	0.0006	0.0029	0.0462	*1.0006*	0.9950 to 1.0062	*0.8299*
LDH	−0.0001	0.0007	0.0137	*0.9999*	0.9985 to 1.0014	*0.9069*
Multivariate						
NLR	0.0856	0.0333	6.6053	*1.0894*	1.0209 to 1.1625	*0.0102*
KPS (80–90 vs 100)	0.5446	0.2412	5.0999	*1.7239*	1.0772 to 2.7590	*0.0239*
ESR	0.0113	0.0084	1.8038	*1.0114*	0.9949 to 1.0282	*0.1793*
d-dimer	0.0000	0.0001	0.4793	*1.0000*	0.9999 to 1.0002	*0.4887*

100) also had a statistically significant association with survival. Variables associated with p value < 0.05 at the univariate analysis were also evaluated in a multivariate Cox-regression model. Among all the selected factors, only KPS and NLR were independently associated with survival, with NLR being the most powerful independent prognosticator (exp(b) 1.09, 95% CI 1.02–1.16, p 0.01) (Table 2).

3.5. Predictive value of NLR

To assess whether NLR would influence the efficacy of oxaliplatin when added to gemcitabine, the effect of the type of chemotherapy on OS was analysed separately in patients with low and high baseline NLR. A significant interaction for OS between NLR and type of chemotherapy was found (test for interaction p-value $\leqslant$ 0.0001), with no difference between GEM and GEMOXA in the low NLR subgroup (mOS 11.8 vs 11.7 months, respectively, p 0.26, Fig. 3A). Conversely, the benefit of GEMOXA doublet was confined only to patients with NLR > 2.5, with a mOS of 9.7 and 3.9 months for GEMOXA vs GEM, respectively, HR 2.08, 95%CI 1.20–3.61, p 0.005 (Fig. 3B).

Moreover, the change of NLR during the first month of chemotherapy correlated with treatment activity, in particular a reduction of NLR was associated with a higher DCR (50% vs 28%, respectively) as determined at the first CT scan reassessment after three months of therapy, with an Odds Ratio of 0.39, p 0.02. The proportion of patients with NLR reduction after chemotherapy was 45% and 53% for GEM and GEMOXA, respectively (chi-squared test p 0.468).

In further confirmation of this, among patients with high baseline NLR, those whose NLR decreased below the cutoff value of 2.5 during chemotherapy had a significantly longer survival than patients who maintained NLR > 2.5 (mOS for patients with low baseline NLR, NLR changing from > 2.5 to < 2.5 and persistent NLR > 2.5 of 9.2, 7.7 and 5.0 months, respectively, p 0.003, Fig. 4).

4. Discussion

In the present study we were able to confirm NLR as a powerful prognostic biomarker in a homogenous set of metastatic PDA patients consisting of

Overall Survival for NLR < 2.5
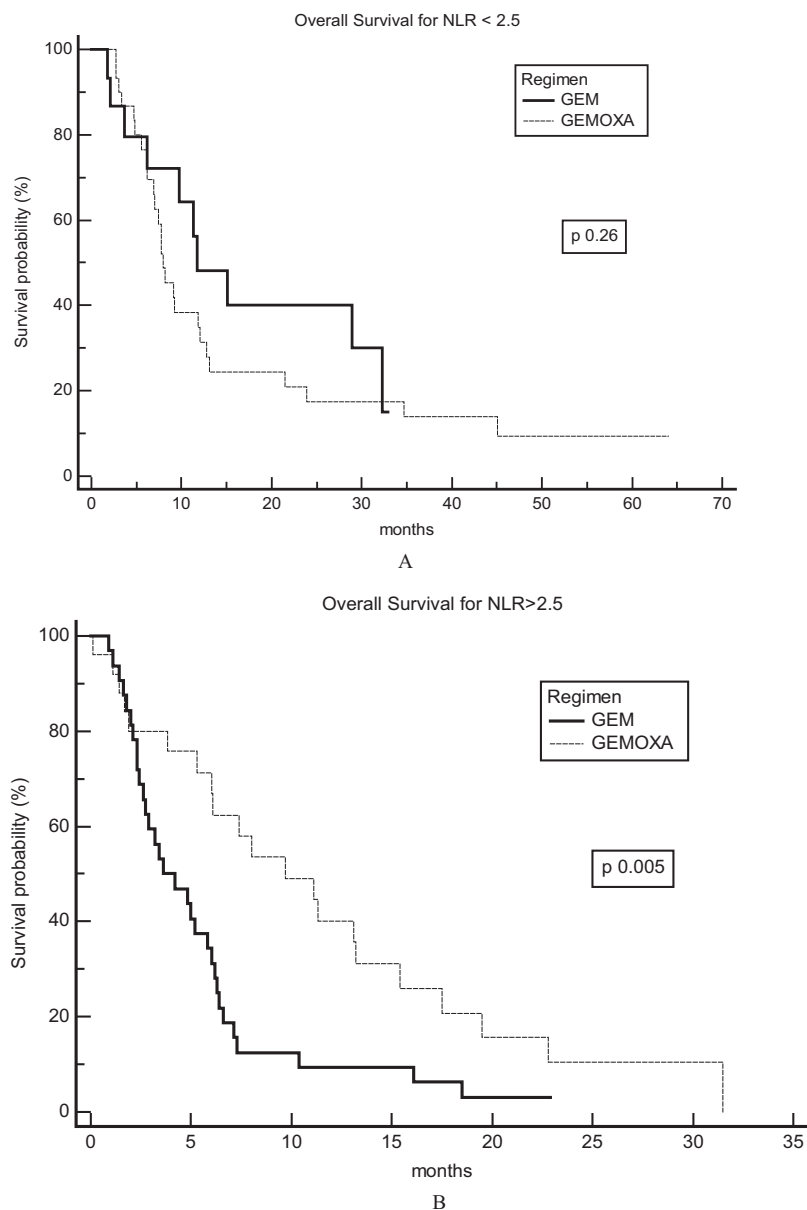

A

Overall Survival for NLR>2.5

B

Fig. 3. Effect of chemotherapy on survival in low (< 2.5) (A) and high (≥ 2.5) (B) baseline neutrophil/lymphocyte ratio (NLR) patients. GEM: gemcitabine monotherapy. GEMOXA; gemcitabine plus oxaliplatin.

two subgroups, the GEM monotherapy group and the GEMOXA group.

Authors acknowledge that this is a single retrospective study and the population enrolled is quite small. Nonetheless, to the best of our knowledge, this is the first report analyzing the predictive role of NLR with regards to oxaliplatin activity in PDA patients. Moreover, we highlighted the clinical relevance of NLR when assessed longitudinally after one month of treatment.

In the whole population, GEMOXA was superior to GEM in terms of OS, with borderline p value (Fig. 1). It cannot be excluded that larger sample size would make significant the GEMOXA superiority in an unselected PDA population. However, two phase III randomized trials (the E6201 and the GERCOR/GISCAD trial, $n = 832$ and 326, respectively), specifically testing this hypothesis, have failed to reach statistical significance [5,8], thus confirming that oxaliplatin may be effective only in a select group of patients. In our uni-
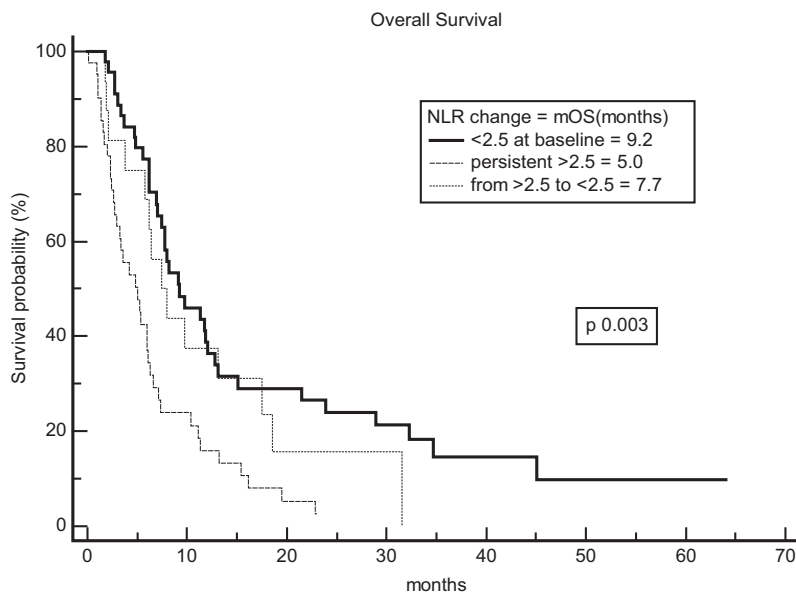
Fig. 4. Overall Survival (OS) and neutrophil/lymphocyte ratio (NLR) change during chemotherapy. mOS: median OS.

variate Cox-regression analysis, the type of chemotherapy was not significantly associated with survival (Table 2). Type of chemotherapy remained not significant even when included in a multivariate analysis together with NLR, KPS, ESR and d-dimer (data not shown). According to our analysis, NLR was the best predictive factor of oxaliplatin efficacy in that GEMOXA was superior to GEM only in the high baseline NLR group.

Furthermore, NLR reduction during chemotherapy correlated with disease control rate (DCR 50% v 28%, p 0.02), and patients with high baseline NLR in whom this variable decreased below the cutoff value of 2.5 during treatment had a survival comparable to that of patients with favourable features.

It can be hypothesized that patients with better prognosis (NLR < 2.5) are more likely to receive oxaliplatin as second-line therapy after gemcitabine monotherapy failure, thus resulting in comparable survival to patients treated with GEMOXA upfront. Conversely, tumors with a more aggressive behaviour (NLR > 2.5) may have a rapid progression on first-line monotherapy (mOS 3.9 months) and second line administration may be precluded. In our cohort, in fact, among GEM monotherapy patients, 48% of those with NLR < 2.5 received a second-line therapy, as compared to 8% of those with NLR > 2.5 (data not shown). In these patients an intensive combination chemotherapy may be more appropriate in the first-line setting.

A number of studies have evaluated the prognostic value of NLR, first in patients with localized PDA candidate for radical surgery and subsequently also in large cohorts including metastatic patients treated with chemotherapy. Following a thorough PubMed search, we found two studies on localized PDA and five studies on metastatic PDA that we thought to be of particular interest.

In a study by Hamed et al., 228 patients with tumor of the periampullary region (pancreatic cancer, ampullary cancer or cholangiocarcima) undergoing pancreatoduodenectomy were retrospectively reviewed. Median survival of patients with NLR < 5 was 24 months, whilst patients with NLR > 5 had a mOS of 13 months. NLR maintained its prognostic value also among patients with disease relapse [29]. In another dataset by Garcea et al., NLR significantly predicted disease free survival (DFS) among radically resected patients with pancreatic cancer. Median DFS was 12 and 52 months for patients with preoperative NLR $>$ or < 5, respectively, $p < 0.001$ [30].

Szkandera et al. reported, in two different papers, the analysis of a large cohort of PDA patients ($n = 474$), most of whom ($n = 344$) received palliative chemotherapy for a stage IV disease. NLR was confirmed to be an independent prognostic biomarker in multivariate analysis, together with tumor stage, grade, administration of chemotherapy and high CRP [31]. NLR cut-off was initially set at 5, according to the previous literature. Later, a ROC analysis was performed and a cut-off value similar to that obtained in our analysis was identified (i.e. NLR 2.3) [32].

Xue et al. have recently reported on 252 Japanese patients with advanced PDA receiving palliative chemotherapy, mainly GEM (70%). No patients received GEMOXA. NLR was confirmed to be an independent prognostic factor. Median survival was longer than that observed in our cohort, maybe owing to the difference in ethnicity (mOS 13.4 and 8.6 months for NLR $>$ and $\leqslant$ 3, respectively, $p < 0.01$) [33].

Other two studies have investigated the prognostic value of NLR in PDA patients treated with gemcitabine-based chemotherapy. In a study by An et al., 95 patients were enrolled, 18% had NLR > 5 and this was associated with a median survival of 2.4 months as compared to 7.7 months for NLR < 5, $p < 0.001$ [34]. Almost half of the patients received GEMOXA (44%), but the possible predictive value of NLR for GEMOXA activity was not analysed. In another dataset by Teo et al., 85 patients (of whom only three patients received GEMOXA) were analysed and NLR > 3 was associated to mOS of 3.4, as compared to 9.4 for patients with NLR < 3, $p = 0.001$ [35]. Median survival in these two reports is comparable to that obtained in our study.

More recently, Luo et al. have confirmed the prognostic value of both baseline NLR and NLR change induced by chemotherapy in 403 patients with advanced pancreatic adenocarcinoma treated with different regimens of chemotherapy. NLR cutoff value was set at 3.1 [36]. NLR was an independent predictor in a multivariable model including serum CA19-9 levels and serum albumin levels. Albumin levels are often analyzed in conjunction with NLR and are included in an inflammatory index known as the Glasgow Prognostic Score (GPS) [37]. In our cohort the variables on which GPS is based (i.e. CRP and albumin) were not significantly associated with survival (Table 2).

We recognize a number of limitations in our study. First of all, as already mentioned, the research was retrospective and sample size was relatively small. Moreover, the analysis of the predictive value of NLR for oxaliplatin efficacy was achieved by dividing further the population in smaller treatment subgroups. Treatment assignment was not carried out upon randomization and this is a major drawback. Even though type of regimen was chosen by criteria other than PS, and the proportion of patients with KPS 80–90 was similar in the GEM and GEMOXA group, a selection bias cannot be ruled out. Randomized trials investigating prospectively the prognostic/predictive value of NLR would be desirable. Moreover the choice of GEMOXA as the preferred doublet in our Institution can be arguable and

the patients' preference for GEM, mainly based on its less toxicity, can be considered 'too subjective' from a methodological point of view. Finally, we had no blood sample available to assess in depth the systemic inflammatory response in our cohort. In particular, some mediators are known to drive the systemic inflammation in cancer patients and may help clarify the biological mechanisms underlying our findings. As an example, circulating cytokines, such as IL-6 and TNF, should be included in future prospective trials analyzing NLR in this setting of patients [38,39].

In conclusion, in light of two recent phase III trials demonstrating the superiority of new combination regimens (i.e. FOLFIRINOX and nab-paclitaxel + gemcitabine) over gemcitabine monotherapy, but with higher toxicity, NLR may represent a readily available and inexpensive test to select patients for whom a particularly poor prognosis would justify the use of these more intensive, yet less tolerable, combination chemotherapy.

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Conflict of interest

Authors have no conflict of interest to declare.

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