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ORIGINAL ARTICLE

Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO

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Background: Neutrophil/lymphocyte ratio (NLR), defined as absolute neutrophils count divided by absolute lymphocytes count, has been reported as poor prognostic factor in several neoplastic diseases but only a few data are available about unresectable metastatic colorectal cancer (mCRC) patients (pts). The aim of our study was to evaluate the prognostic and predictive role of NLR in the TRIBE trial.

Patients and methods: Pts enrolled in TRIBE trial were included. TRIBE is a multicentre phase III trial randomizing unresectable and previously untreated mCRC pts to receive FOLFOXIRI or FOLFIRI plus bevacizumab. A cut-off value of 3 was adopted to discriminate pts with low (NLR < 3) versus high (NLR ≥ 3) NLR, as primary analysis. As secondary analysis, NLR was treated as an ordinal variable with three levels based on terciles distribution.

Results: NLR at baseline was available for 413 patients. After multiple imputation at univariate analysis, patients with high NLR had significantly shorter progression-free survival (PFS) [hazard ratio (HR) 1.27 (95% CI 1.05–1.55), $P = 0.017$] and overall survival (OS) [HR 1.56 (95% CI 1.25–1.95), $P < 0.001$] than patients with low NLR. In the multivariable model, NLR retained a significant association with OS [HR 1.44 (95% CI 1.14–1.82), $P = 0.014$] but not with PFS [HR 1.18 (95% CI 0.95–1.46), $P = 0.375$]. No interaction effect between treatment arm and NLR was evident in terms of PFS (P for interaction $= 0.536$) or OS (P for interaction $= 0.831$). Patients with low [HR 0.84 (95% CI 0.64–1.08)] and high [HR 0.73 (95% CI 0.54–0.97)] NLR achieved similar PFS benefit from the triplet and consistent results were obtained in terms of OS [HR 0.83 (95% CI 0.62–1.12) for low NLR; HR 0.82 (95% CI 0.59–1.12) for high NLR].

Conclusion: This study confirmed the prognostic role of NLR in mCRC pts treated with bevacizumab plus chemotherapy in the first line, showing the worse prognosis of pts with high NLR. The advantage of the triplet is independent of NLR at baseline.

Key words: neutrophil/lymphocyte ratio, prognostic factor, metastatic colorectal cancer, cancer inflammation, FOLFOXIRI plus bevacizumab

Introduction

Despite the importance of molecular and biological features in defining the prognosis of cancer patients, several studies suggest the contribution of the host-driven inflammatory response to tumours' behaviour and treatments' outcome [1, 2].

In fact, tumour growth and metastatic spread result from several interactions between tumoural and stromal factors, including blood vessels, inflammatory cells and immunity system, leading to a chronic inflammation [3, 4].

Laboratory markers of systemic inflammatory response, such as C-reactive protein (CRP), hypoalbuminemia, Glasgow Prognostic Score (combining CRP and albumin levels), white blood cell count, neutrophil/lymphocyte ratio (NLR) or platelets/lymphocytes ratio, have been studied as prognostic and predictive factors in several tumours [5, 6].

NLR, defined as the absolute neutrophils count divided by the absolute lymphocytes count [6–8], has been reported as a poor prognostic factor in several neoplastic diseases, such as breast cancer [9] stomach, pancreatic cancer and hepatocellular carcinoma [10–12].

The role of inflammation markers in predicting prognosis of colorectal cancer patients has been clearly evidenced in radically resected patients [5] and more recently suggested also in the metastatic setting [13–18].

In metastatic colorectal cancer (mCRC) patients with liver-limited disease undergoing radical resection of metastasis following neo-adjuvant therapy, high NLR seems to predict worse outcome. Interestingly, patients with a normalized NLR after neoadjuvant chemotherapy showed similar 1-, 3- and 5-year survival compared with patients with low NLR at baseline [19].

TRIBE was a multicentre phase III trial randomizing unresectable and previously untreated mCRC patients to receive the triplet FOLFOXIRI plus bevacizumab or the doublet FOLFIRI plus bevacizumab. Longer progression-free survival (PFS) [median PFS 12.1 versus 9.7 months; hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.62–0.90; $P = 0.003$], overall survival (OS) (median OS 29.8 versus 25.8 months; HR 0.80, 95% CI 0.65–0.98; $P = 0.03$) and better objective response rate (65% versus 53%; $P = 0.006$) were reported with the triplet plus bevacizumab [20]. Other trials more recently investigated the effect of the intensification of the chemotherapy with the triplet as compared with a standard doublet with consistent results in terms of both efficacy and toxicity (STEAM and CHARTA) [21, 22]. By a clinical perspective, these data not only support the choice of FOLFOXIRI plus bevacizumab as a potential first-line option for mCRC patients but also open the way to the need of identifying those who may derive more benefit from an intensified approach.

The aim of this analysis was evaluating the prognostic and predictive role of NLR in mCRC patients treated with first-line FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab in the TRIBE trial.

In particular, we asked whether NLR could represent a reliable tool to select the best candidates to an intensified chemotherapy backbone.

Patients and methods

Study population

TRIBE (a phase III randomized trial of FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first- line treatment of mCRC; NCT00719797) [23] was a prospective, open-label, multicentre phase III randomized study conducted in 34 Italian centres, in which unresectable mCRC patients were assigned in a 1 : 1 ratio to receive FOLFIRI plus bevacizumab (control group, $N = 256$) or FOLFOXIRI plus bevacizumab (experimental group, $N = 252$). Treatment was continued up to 12 cycles and, if disease stability or response were obtained, maintenance with bevacizumab plus 5-fluoruracil/folinic acid was administered until progression, unacceptable toxicity or informed consent withdrawal.

Key eligibility criteria included histologically confirmed diagnosis of colorectal adenocarcinoma, age between 18 and 75 years, ECOG PS of ≤ 2 (0 for patients between 71 and 75 years old), first occurrence of metastatic disease deemed unresectable, and measurable disease according to RECIST.

The protocol was approved by local Ethics Committees at participating centres and patients provided their written informed consent to receive the treatment and to participate to translational analyses.

Tumour response was evaluated every 8 weeks by means of contrast enhanced computed tomography scan according to RECIST v1.0.

Statistical analysis

NLR was defined as the absolute neutrophils count divided by the absolute lymphocytes count. Neutrophils and lymphocytes counts collected within 28 days before randomization were taken into consideration. To avoid the exclusion of cases with missing data, the multiple imputation method was used (10 imputations). Regression method was used for imputation of NLR values. Missing-at-random assumption was made.

A cut-off value of 3 was adopted to discriminate patients with low (NLR <3) versus high (NLR ≥ 3) NLR, as primary analysis. This stratification criterion was also confirmed by the optimal cut point value determination carried out according to Contal and O'Quigley [24].

As secondary analysis, NLR was also treated as an ordinal variable with three levels based on terciles distribution.

The association between NLR and time to event variables was analysed in univariate and multivariate settings using the Cox proportional hazards model. The associations between NLR and response and between NLR and secondary R0 resection were assessed using a logistic model. Results of the analyses of imputations were combined according to Rubin's procedure [25].

The predictive role of NLR for the effect of the treatment was investigated by means of interaction test. PFS and OS curves were estimated with the Kaplan–Meier method and results from multiple imputation analysis were summarized according to Rubin's rules after complementary log transformation [26]. All statistical tests were two sided, and P values of ≤ 0.05 were considered statistically significant. Statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Out of 508 patients enrolled in the TRIBE trial, NLR at baseline was available for 413 patients (data were missing for the remaining 95 patients); 207 (50.1%) and 206 (49.9%) in the FOLFIRI plus bevacizumab and FOLFOXIRI plus bevacizumab arm, respectively. According to the specified cut-off (NLR <3 versus ≥ 3), 235 (56.9%) and 178 (43.1%) patients had low and high NLR, respectively. After multiple imputation, median NLR was 2.75 (interquartile range 1.94–3.82), with median values for first, second and third terciles of 1.72, 2.75 and 4.37, respectively.

Main patients' characteristics at baseline are summarized in Table 1.

At a median follow-up of 48.1 months, the 468 patients (92%) progressed and 374 (74%) died.

Table 1. Patients' characteristics at baseline in the neutrophil/lymphocyte ratio (NLR) evaluable and missing population and according to NLR value

Characteristics	Overall population ($N = 508$)	NLR evaluable population ($N = 413$)	NLR missing population ($N = 95$)	NLR <3 ($N = 235$)	NLR ≥ 3 ($N = 178$)
Age					
Median	60	61	60	60	59
Range	29–75	29–75	33–75	29–75	29–75
Gender (%)					
Male	60	59	65	58	63
Female	40	41	35	42	37
ECOG PS (%)					
0	90	90	87	92	87
1–2	10	10	13	8	13
Site of primary tumour (%)					
Right colon	31	30	37	28	35
Left colon/rectum	69	70	63	72	65
Previous adjuvant therapy (%)					
No	87	88	83	86	90
Yes	13	12	17	14	10
Time to metastases (%)					
Synchronous	80	80	80	77	84
Metachronous	20	20	20	23	16
Metastases (%)					
Confined to liver	21	21	20	23	17
Not confined to liver	79	79	80	77	83
Resected primary tumour (%)					
Yes	67	67	67	73	59
No	33	33	33	27	41
Kohne score (%)					
High risk	10	10	10	8	13
Intermediate risk	45	46	48	45	46
Low risk	45	44	42	47	41
RAS/BRAF status (%)					
RAS and *BRAF* wild-type	26	26	25	25	28
RAS mutated	66	66	66	66	66
BRAF mutated	8	8	9	8	8
Arm (%)					
FOLFIRI plus bev	50	50	52	51	49
FOLFOXIRI plus bev	50	50	48	49	51

In terms of prognostic impact, at univariate analysis, patients with high NLR had significantly shorter PFS [HR 1.27 (95% CI 1.05–1.55), $P = 0.017$] and OS [HR 1.56 (95% CI 1.25–1.95), $P < 0.001$] than patients with low NLR. Stratifying the study population on the terciles of NLR, significant associations of NLR with both PFS ($P = 0.009$) and OS ($P < 0.001$) were found (Table 2).

In the multivariable model, including age, ECOG PS, the prior exposure to an adjuvant treatment, primary tumour location, time to metastases, liver-limited extent of disease, resection of the primary tumour, Kohne prognostic score [27] and *RAS*/*BRAF* mutational status as covariates, the NLR retained a significant association with OS [HR 1.44 (95% CI 1.14–1.82), $P = 0.014$] but not with PFS [HR 1.18 (95% CI 0.95–1.46), $P = 0.375$], while treatment with FOLFOXIRI plus bevacizumab was still associated with better outcome than FOLFIRI plus bevacizumab in terms of both PFS [HR 0.76 (95% CI 0.63–0.92), $P = 0.005$] and OS [HR 0.75 (95% CI 0.60–0.93), $P = 0.009$] (Table 3).

Patients with high NLR also showed lower response rate both in the univariable [odds ratio (OR) 0.53 (95% CI 0.36–0.80), $P = 0.003$] and multivariable models [OR 0.55 (95% CI 0.36–0.84), $P = 0.006$], where FOLFOXIRI plus bevacizumab was still associated with higher response rate [OR 1.65 (95% CI 1.12–2.41), $P = 0.010$] (supplementary Table S1, available at *Annals of Oncology* online). No impact of NLR on the probability of achieving R0 resections of metastatic lesions was evident at the univariate analysis [OR 0.62 (95% CI 0.34–1.14), $P = 0.124$] or in the multivariable model [OR 0.67 (95% CI 0.33–1.36), $P = 0.285$] (supplementary Table S1, available at *Annals of Oncology* online).

No interaction effect between treatment arm and NLR was evident in terms of PFS (P for interaction = 0.536), OS (P for interaction = 0.831), response (P for interaction = 0.552) and R0 resection rate (P for interaction = 0.402). Patients with low [HR 0.84 (95% CI 0.64–1.08)] and high [HR 0.73 (0.54–0.97)] NLR achieved similar PFS benefit from the intensification of the chemotherapy backbone and consistent results were obtained in

Table 2. Prognostic impact of neutrophil/lymphocyte ratio (NLR)

N = 508 random	*N* = 413	HR for PFS (95% CI)	*P*	HR for OS (95% CI)	*P*
NLR					
<3	235 (57%)	1	0.017	1	<0.001
≥3	178 (43%)	1.27 (1.05–1.55)		1.56 (1.25–1.95)	
NLR					
2° versus 1° tercile		0.91 (0.72–1.14)	0.009	1.07 (0.81–1.40)	<0.001
3° versus 1° tercile		1.31 (1.03–1.65)		1.65 (1.26–2.16)	

HR, hazard ratio; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Table 3. Association of neutrophil/lymphocyte ratio (NLR) with progression-free survival (PFS) and overall survival (OS): multivariable analysis

N = 508		HR for PFS (95% CI)	*P*	HR for OS (95% CI)	*P*
Arm	FOLFOXIRI + bev versus FOLFIRI + bev	0.76 (0.63–0.92)	0.005	0.75 (0.60–0.93)	0.009
Age	≥65 versus <65	1.04 (0.85–1.28)	0.699	1.33 (1.06–1.66)	0.014
PS	1–2 versus 0	1.63 (1.21–2.22)	0.003	2.32 (1.68–3.19)	<0.001
Prior adjuv	Yes versus no	1.17 (0.75–1.84)	0.491	1.06 (0.62–1.81)	0.833
Site of prim	Left versus right	0.89 (0.72–1.11)	0.333	0.78 (0.61–1.00)	0.057
Time to mets	Metachr versus Synchr	0.66 (0.45–0.98)	0.033	0.59 (0.38–0.92)	0.014
Liver-only	No versus yes	1.21 (0.88–1.66)	0.255	0.81 (0.62–1.05)	0.596
Primary resected	Yes versus no	0.90 (0.71–1.15)	0.410	0.81 (0.62–1.05)	0.118
NLR	≥3 versus <3	1.18 (0.95–1.46)	0.375	1.44 (1.14–1.82)	0.014
Kohne score	Intermediate versus low	1.13 (0.88–1.46)	0.011	1.14 (0.85–1.52)	0.002
	High versus low	1.79 (1.23–2.60)		2.07 (1.38–3.09)	
RAS/BRAF	*RAS* mut versus *RAS/BRAF* wt	1.09 (0.75–1.58)	0.013	1.16 (0.85–1.57)	0.124
	BRAF mut versus *RAS/BRAF* wt	1.71 (1.14–2.56)		1.73 (0.89–3.37)	

HR, hazard ratio; CI, confidence interval.

terms of OS [HR 0.83 (95% CI 0.62–1.12) in patients with low NLR and HR 0.82 (95% CI 0.59–1.12) in patients with high NLR] (Figures 1 and 2).

Discussion

The identification of prognostic and predictive factors to chemotherapy and biological treatment is crucial in the choice of the therapy of mCRC, especially considering the available schedules and the objective of personalizing, as more as possible, the treatment. There is growing evidence about the stroma–tumour interaction, its involvement in the carcinogenesis process and tumour progression, as a result of a chronic inflammatory state [3, 4]. In order to deepen the potential impact of surrogate markers of this inflammatory reaction in mCRC, NLR, has been studied as a potential prognostic factor in patients treated with first-line doublets of chemotherapy. The NLR cut-off used more often were 3 or 5 [14, 15]; for this reason, between 3 and 5, we decided to use the cut-off closer to the median value. In 2014, the TRIBE trial showed that the intensification of treatment with FOLFOXIRI plus bevacizumab adds significant benefit in terms of survival and response in mCRC patients compared with the doublets plus bevacizumab [23].

Here, we show that NLR at baseline has an independent prognostic impact in patients treated in first-line with chemotherapy and bevacizumab, with a worse prognosis in patients with NLR ≥3 than those with NLR <3, in the univariate analysis and in the multivariate but, in the latter, with a significant association only with OS and response rate.

The mechanism underlying the association between high NLR and worse outcome has not been cleared, but it could be due to the association of NLR with inflammation. Indeed, neutrophilia can inhibit the immune system, abolishing the cytolytic activity of immune cells [28, 29]. At the same time, both tumour cells and host cell, including neutrophils, can produce chemokines and cytokines, thus contributing to tumour progression [3].

High NLR is also associated with increased peritumoral infiltrate of macrophages and increased production of interleukin (IL)-17 [30]. Neutrophils and other cells, including macrophages, produce factors able to promote tumour growth, such as vascular endothelial growth factor [31, 32], hepatocyte growth factor [31] and IL-6 [33], also involved in increased CRP and reduced albumin synthesis [34]. These are both prognostic factors

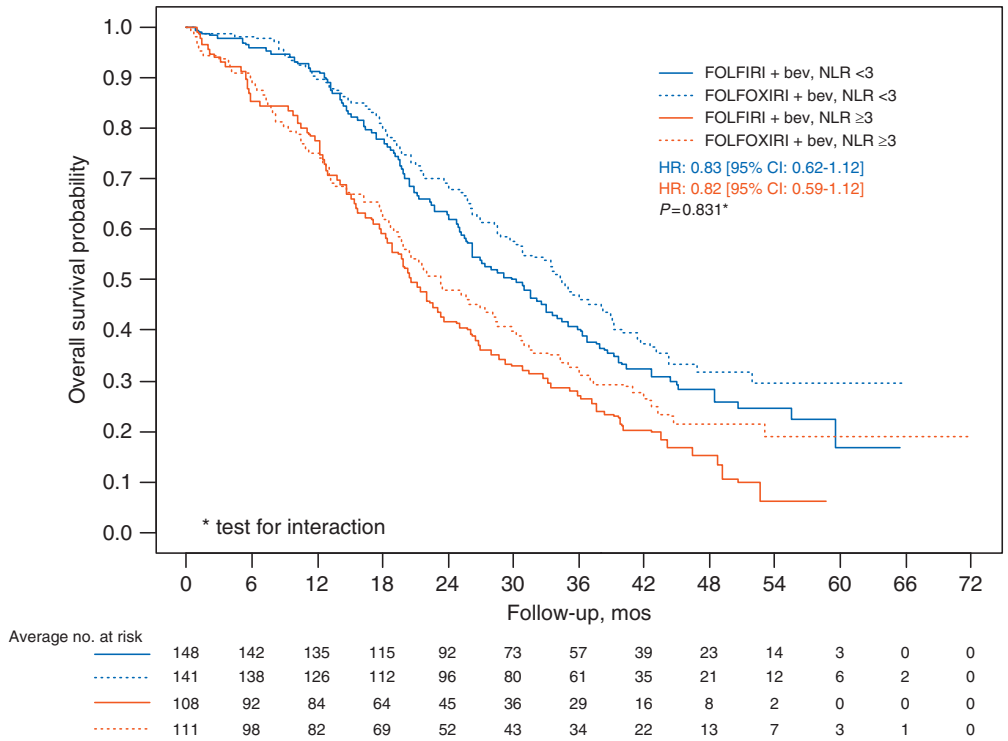

Figure 1. Kaplan–Meier estimates of overall survival (OS) according to neutrophil/lymphocyte ratio (NLR) and treatment arm.

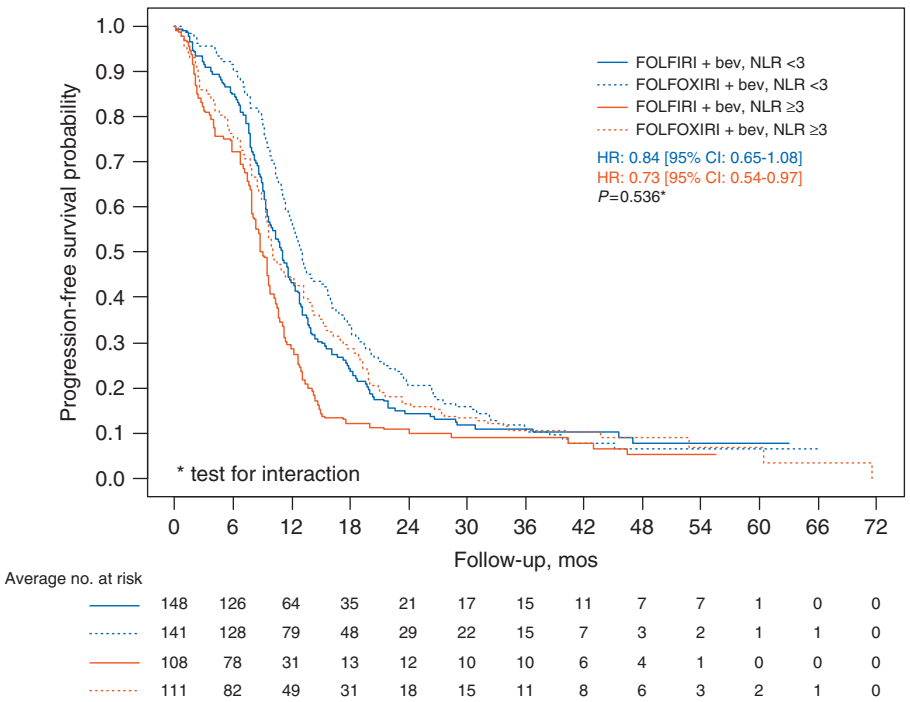

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS) according to neutrophil/lymphocyte ratio (NLR) and treatment arm.

included in the Glasgow Prognostic Score and the latter one is a negative prognostic factor in several solid tumours [35]. On the other hand, lymphocytopenia is frequently found in patients with advanced disease, indicating an immunosuppression state [14, 36]. This might be due to the higher susceptibility of lymphocyte T to apoptosis, caused by a chronic state of activation in solid tumours [37, 38] determining lower immune activity on tumour antigens released by cancer cells during chemotherapy [39].

However, it should be recognized that neutrophils and lymphocytes counts are non-specific parameters, because they could

be influenced by concomitant conditions, such as infections or inflammation [40].

The strength of our cohort relies in the collection of patients' data enrolled in a prospective study, in which patients were clinically selected to be included, because they were candidates to an intensive chemotherapy regimen, such as the triplet. To this end, no predictive impact of baseline NLR was evident with regard to the intensification of the upfront chemotherapy regimen both in the univariate analysis and in the multivariable model.

Conclusion

The impact of FOLFOXIRI plus bevacizumab seems therefore independent from NLR, and the advantage of the triplet versus the doublet is confirmed also in the poor prognosis subgroup of patients with high NLR at baseline. These data strengthen the potential role of FOLFOXIRI plus bevacizumab as upfront treatment, able to counteract the impact of negative prognostic factors but do not allow identifying NLR as a criterion to select those patients who may derive more benefit from this intensified treatment.

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Disclosure

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