Prognostic value of the neutrophil-to-lymphocyte ratio in advanced hepatocellular carcinoma: an exploratory analysis from the ARQ 197-215 study

706 P

Nicola Personeni[1, 2], Laura Giordano[1], Giovanni Abbadessa[3], Camillo Porta[4], Ivan Borbath[5], Bruno Daniele[6], Stefania Salvagni[7], Jean Luc Van Laethem[8], Hans Van Vlierberghe[9], Joerg Trojan[10], Enrico N. De Toni[11], Alan Weiss[12], Steven Miles[13], Antonio Gasbarrini [14], Monica Lencioni[15], Maria E. Lamar[16], Yunxia Wang[17], Dale Schuster[18], Brian Schwartz[16], Armando Santoro[1,19], Lorenza Rimassa[1]

1.Humanitas Cancer Center, Humanitas Clinical and Research Center, Rozzano, Italy, 2.Department of Medical Biotechnology and Translational Medicine, University of Milan, Italy, 3.Clinical Development & Translational Medicine, ArQule, Burlington, MA, United States, 4.Oncologia Medica, Fondazione IRCCS Policlinico Universitario San Matteo, Pavia, Italy, 5.Gastro-entérologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium, 6.Oncology, G. Rummo Hospital, Benevento, 7.Oncologia Medica, Azienda Ospedaliera Parma, Parma, Italy, 8.Gastro-entérologie, Erasme University Hospital, Brussels, 9.Gastro-entérologie, Ghent University Hospital, Gent, Belgium, 10.Internal Medicine, J. W. Goethe University Hospital, Frankfurt, 11.Medicine II, Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany, 12.Gastroenterology, Vancouver General Hospital and British Columbia Cancer Clinic, Vancouver, Canada, 13.Oncology, Cedar Sinai, Los Angeles, CA, United States, 14.Patologia Speciale Medica e Semeiotica Medica, Policlinico Universitario Agostino Gemelli, Rome, 15.Oncology, Azienda Ospedaliero-Universitaria di Pisa, Pisa, Italy, 16.Clinical Development, 17.Pharmacology, ArQule, Burlington, MA, United States, 18.Clinical Development, Daiichi-Sankyo, Edison, NJ, United States, 19.Humanitas University, Rozzano, Italy

Background

Hepatocellular carcinoma (HCC) represents the most common primary liver cancer with an increasing incidence.

Neutrophil-to-lymphocyte ratio (NLR) is a readily available marker for assessing the systemic inflammatory changes. NLR reflects the potential balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent anti-tumor immune function.

A recent review and meta-analysis showed that NLR in HCC patients treated with different therapeutic modalities is associated with overall survival [1]. However, most evidences in the advanced setting include retrospective series relying on limited numbers of patients.

The ARQ 197-215 was a randomized placebo-controlled phase II study testing the MET inhibitor tivantinib in second-line HCC patients. Further analyses [2] clarified the role of MET expression and additional circulating biomarkers either as predictors of treatment efficacy or prognostic factors.

Herein, we evaluated the potential role of NLR as predictors of outcome in HCC patients treated in the frame of the ARQ197-215 study [3].

Table 1. Baseline characteristics of the study participants: comparison between the low (≤3) and high (>3) NLR populations

Group	All patients		NLR ≤ 3		NLR > 3		p value
	N	%	N	%	N	%	
Treatment							
Placebo	33	33.7	18	36.7	15	30.6	0.521
Tivantinib	65	66.7	31	63.3	34	69.4	
Vascular invasion							
No	64	65.3	33	51.6	31	48.4	0.671
Yes	34	34.7	16	47.1	18	52.9	
Distant metastases							
No	33	33.7	18	54.5	15	45.5	0.521
Yes	65	66.3	31	47.7	34	52.3	
Baseline AFP							
≤ Median	47	48.0	23	48.9	24	48.9	0.837
> Median	47	48.0	24	51.1	23	51.1	
Missing	4	4.0					
Met expression							
Low	35	35.7	19	54.3	16	45.7	0.552
High	36	36.7	17	47.2	19	52,8	

Patients and methods

patients and trial design

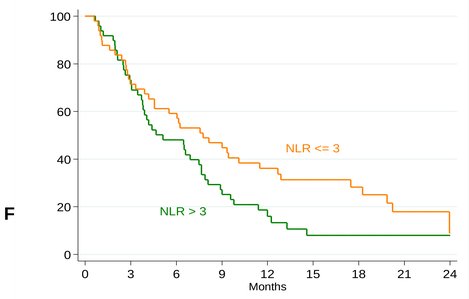
The eligible population for the current exploratory analysis included all ARQ 197-215 [3] participants with available WBC, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) data at the day 1 of the first treatment cycle (before commencement of therapy). The NLR was calculated using the standard formula: NLR = ANC/ALC

statistical methods

Patients were grouped into 'high' and 'low' NLR populations based upon a pre-defined cut-off value of 3.0. Kaplan–Meier method was used to estimate and plot survival end points. A Cox proportional hazard model was used to assess association between baseline NLR and survival end points. Interactions between treatment group and NLR level were included in the Cox proportional hazard model.

Results

After a median follow up of 18.9 months (range 0.6-24.8) median **OS** was 5.1 months in patients with NLR >3 and 7.8 months in patients with NLR ≤3 (p = 0.044).



Median **TTP** in both NLR groups was 1.4 month (p = 0.10)

multivariable analysis

The Cox multivariable analysis confirmed that only NLR and vascular invasion were independent predictors of survival in the all-patient cohort. In this model, NLR ≥3 was associated with an adjusted HR of 1.65 (95% CI 1.05–2.59; p = 0.03), and macrovascular invasion also was negatively associated with OS (HR 1.74; 95% CI 1.10–2.75; p = 0.017).

long-term survivors

There were 22 long-term survivors, defined as patients surviving beyond 12 months. Of these, 16 (72.7%) had low NLR compared with 6 (27.2%) with high NLR. This equated to 32.6% (16 of 49) of all patients with a low NLR achieving survival beyond 12 months compared with only 12.2% (6 of 49) of all patients with a high NLR. A Chi-squared test confirmed an association between low baseline NLR and long-term survival (p = 0.015).

Table 2. Association between NLR and patient outcomes within the two treatment groups of the ARQ 197-215 study

	NLR (continuous variable)		
	HR	CI 95%	p value
Overall survival			
Placebo	1.3	1.08-1.57	0.006
Tivantinib	1.16	1.00-1.34	0.049
Time to progression			
Placebo	1.18	1.00-1.40	0.058
Tivantinib	1.04	0.91-1.20	0.538

Conclusions

- NLR is an independent predictor of OS for patients with HCC who are candidates to second-line treatment.
- The test for interaction between NLR and treatment was not statistically significant.
- MET expression is the only biomarker predicting tivantinib efficacy in advanced HCC [2].
- Our results extend previously published retrospective observations [1] in the frame of a prospective, placebo-controlled randomized trial for advanced HCC.
- The low cost, easy determination, and reproducibility of a full blood count make NLR a promising tool for assessing HCC prognosis in future clinical practice.

Bibliography

1. Qi X, et al. Oncotarget. 2016 Jun 10. doi: 10.18632/oncotarget.9942.
2. Rimassa L, et al. Oncotarget. 2016 Aug 25. doi: 10.18632/oncotarget.11621.
3. Santoro A, et al. Lancet Oncol. 2013 Jan;14(1):55-63.

Supported by: ArQule, Inc, and Daiichi-Sankyo

Email: nicola.personeni@cancercenter.humanitas.it