ANTICANCER RESEARCH *41*: 3131-3137 (2021)
doi:10.21873/anticanres.15098

The Pre-treatment Lymphocyte-to-Monocyte Ratio Predicts Efficacy in Metastatic Colorectal Cancer Treated With TAS-102 and Bevacizumab

HIDEKAZU KURAMOCHI[1], TAKESHI YAMADA[2], YOICHIRO YOSHIDA[3], AKIHISA MATSUDA[2], HIROHIKO KAMIYAMA[4], CHIHIRO KOSUGI[5], KEIICHIRO ISHIBASHI[6], ATSUKO FUKAZAWA[7], KEISUKE IHARA[8], HIROMICHI SONODA[2], KAZUHIKO YOSHIMATSU[9], HIROSHI YOSHIDA[2], SUGURU HASEGAWA[3], KAZUHIRO SAKAMOTO[4], HIDEYUKI ISHIDA[6] and KEIJI KODA[5]
On behalf of the TAS CC3 Study Group

[1]*Department of Chemotherapy, Tokyo Women's Medical University, Yachiyo Medical Center, Yachiyo, Japan;*
[2]*Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan;*
[3]*Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan;*
[4]*Department of Coloproctological Surgery, Juntendo University Faculty of Medicine, Tokyo, Japan;*
[5]*Department of Surgery, Teikyo University Chiba Medical Center, Ichihara, Japan;*
[6]*Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan;*
[7]*Department of Gastroenterological Surgery, Iwata City Hospital, Iwata, Japan;*
[8]*First Department of Surgery, Dokkyo Medical University, Mibu, Japan;*
[9]*Department of Digestive Surgery, Kawasaki Medical School, Kurashiki, Japan*

Abstract. *Background/Aim: Our multicenter phase II TAS-CC3 study demonstrated favorable median progression-free survival (PFS) and overall survival (OS) of 32 metastatic colorectal cancer (mCRC) patients treated with TAS-102 + bevacizumab as 3rd-line treatment. Patients and Methods: We investigated the predictive and prognostic values of pre-treatment blood inflammation-based scores, including the neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR) and lymphocyte-to-monocyte ratio (LMR) on disease-control (DC), PFS and OS by a post-hoc analysis. Results: Receiver operating characteristic curve analyses of the 3 inflammation-based scores versus DC showed the best predictive performance for LMR, followed by NLR and PLR. The high-LMR group had a significantly higher DC rate than the low group (87.5 vs. 43.8%). The high-LMR group showed significantly longer survival than the low group (4.9 vs. 2.3 m for median PFS) (21.0 vs. 6.1 m for median OS). Conclusion: The pre-treatment LMR is a valid predictive and prognostic biomarker for mCRC patients undergoing TAS-102 and bevacizumab treatment.*

Correspondence to: Takeshi Yamada, Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan. Tel: +81 338222131, Fax: +81 356850989, e-mail: y-tak@nms.ac.jp

Key Words: TAS-102, bevacizumab, colorectal cancer, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR).

TAS-102 is an oral anticancer agent comprising trifluridine (FTD) and tipiracil hydrochloride (1). For patients with metastatic colorectal cancer (mCRC), significantly better progression-free survival (PFS) and overall survival (OS) were shown in those treated with TAS-102 than in those treated with placebo in the global phase III RECOURSE trial (2). Additionally, the combination therapy of TAS-102 and bevacizumab was reported to show favorable PFS in the phase II C-TASK FORCE trial (3). We also previously reported that our single-arm multicenter phase II trial (TAS-CC03 study) using the combination of TAS-102 and bevacizumab showed comparable favorable PFS (4.5 months) and OS (9.3 months) as 3rd-line treatment for patients with mCRC (4). Several previous single-arm phase II studies, including our study, supported the benefit of adding bevacizumab to TAS-102 (3-6). Additionally, a recent randomized phase II trial demonstrated that the combination of TAS-102 and bevacizumab significantly improved PFS compared with TAS-102 alone in mCRC patients (7). Although a large phase III study has not been performed yet, the combination therapy of TAS102 and bevacizumab is a new salvage chemotherapy option for mCRC. Thus, practical

predictors for the efficacy and prognostic markers are warranted.

Inflammation-based indicators, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), C-reactive protein (CRP), and modified Glasgow prognostic score (mGPS), have been widely used as prognostic factors for the oncologic outcomes of cancer treatment. We previously reported the relationship between NLR and survival after TAS-102 treatment (8). In this study, we investigated the association of these inflammation-based indicators with the efficacy of TAS-102 and bevacizumab treatment using the data of patients registered in the TAS-CC3 study to determine whether these indicators predicted the treatment efficacy and prognosis of the patients.

Patients and Methods

Study design and patient population. We performed a post hoc analysis of a prospective investigator-initiated, open-label, single-arm, multicentered phase II study (TAS-CC3) in Japan comprising 32 mCRC patients treated with the combination of TAS102 and bevacizumab as 3rd-line therapy. Patients who were administered first- and second-line chemotherapy and whose tumors were diagnosed as progressive disease were treated with TAS-102 (orally administered at a dose of 35 mg/m^2 twice daily on days 1-5 and 8-12 of every 28-day cycle) plus bevacizumab (5.0 mg/kg by intravenous infusion on days 1 and 15). Tumor response was evaluated by one investigator using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, in patients with measurable disease at baseline. Adverse events were assessed using the Common Terminology Criteria for Adverse Events ver. 4.0 (CTCAE ver. 4.0). Clinical evaluations and computed tomography (CT) scans were performed 8 (±2) weeks after starting chemotherapy and then every 8 (±2) weeks until progression. This study was conducted in accordance with the Declaration of Helsinki and was registered at the University Hospital Medical Information Network as UMIN#000022438.

The white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts were routinely measured at a central laboratory, and the pre-treatment NLR, PLR, and LMR were calculated for each patient. These parameters were divided into two groups (high and low) using as cut-offs the median values.

Statistical analysis. The primary endpoint of TAS-CC3 study was PFS. Secondary endpoints were the time to treatment failure (TTF), response rate, and OS. The median PFS and OS were calculated using the Kaplan–Meier method. Differences in survival between the two patient groups were evaluated using the log-rank test. Spearman's correlation analysis was conducted to examine the correlation between LMR and PFS, OS. Receiver operating characteristic (ROC) curve analysis was conducted to determine the predictive performance of the three inflammation-based scores in tumor response. Continuous variables were expressed as medians and ranges. Variables in univariate analysis for which $p<0.1$ were entered into multivariate Cox proportional hazard models. *p*-Values less than 0.05 were considered significant. All the statistical analyses were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Table I. *Characteristics of the included patients*.

	All cases (n=32)
Age [yrs (range)]	66.5 (45-78)
Gender (male/female)	20 (63%)/12 (38%)
Tumor location (colon/rectum)	18 (56%)/14 (44%)
Sidedness (right/left)	11 (34%)/21 (66%)
ECOG PS (0/1)	23 (72%)/9 (28%)
RAS (wild/mutant)	14 (44%)/18 (56%)
Histology (tub/por/muc)	29 (91%)/1 (3%)/2 (6%)
No of metastasized sites (1/≥2)	11 (37%)/21 (66%)
Metastasized sites	
Liver	22 (69%)
Lung	22 (69%)
Lymph node	7 (22%)
Local	2 (6%)
Peritoneum	1 (3%)
No. of treatment courses (range)	4 (2-24)
Treatment duration (days: range)	129 (49-849)
Bevacizumab (prior/naïve)	32 (100%)/0 (0%)
Subsequent chemotherapy (yes/no)	15 (47%)/17 (53%)
Pre-treatment NLR [median(range)]	2.67 (1.21-10.56)
Pre-treatment PLR [median(range)]	135.2 (55.2-589.5)
Pre-treatment LMR [median(range)]	3.18 (0.83-7.40)

NLR: Neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.

Results

Summary of the TAS CC03 study. Thirty-two patients (median age: 67 years, range=45-78 years) were enrolled in the TAS-CC03 study from June 2016 to August 2017. All the patients were treated with 3rd-line chemotherapy and had a history of receiving bevacizumab in previous lines. The characteristics of patients are shown in Table I. The median number of treatment cycles was four. A partial response was observed in 2 patients, and the disease control (DC) rate was 65.6%. The median PFS was 4.5 months [95% confidence interval (CI)=1.8-7.1], and the median OS was 9.2 months (95%CI=5.5-12.8) as previously reported (4). The pre-treatment median values of NLR, LMR, and PLR were 2.67, 3.18, and 135.2, respectively.

ROC curve analysis. In this post hoc analysis, ROC curve analyses of the three pre-treatment inflammation-based scores, NLR, PLR, and LMR, *versus* DC according to the RECIST criteria showed a best predictive performance in LMR, followed by NLR and PLR (AUC: 0.88, 0.85, and 0.68, respectively) (Figure 1).

LMR, tumor response and adverse events. Table II shows the efficacy and safety profiles according to LMR. The high-LMR group had a significantly higher DC rate than the low group (87.5 *vs*. 43.8%). Two patients with partial responses were in the high-LMR group. No significant association was observed between LMR and adverse events (≥grade 3).

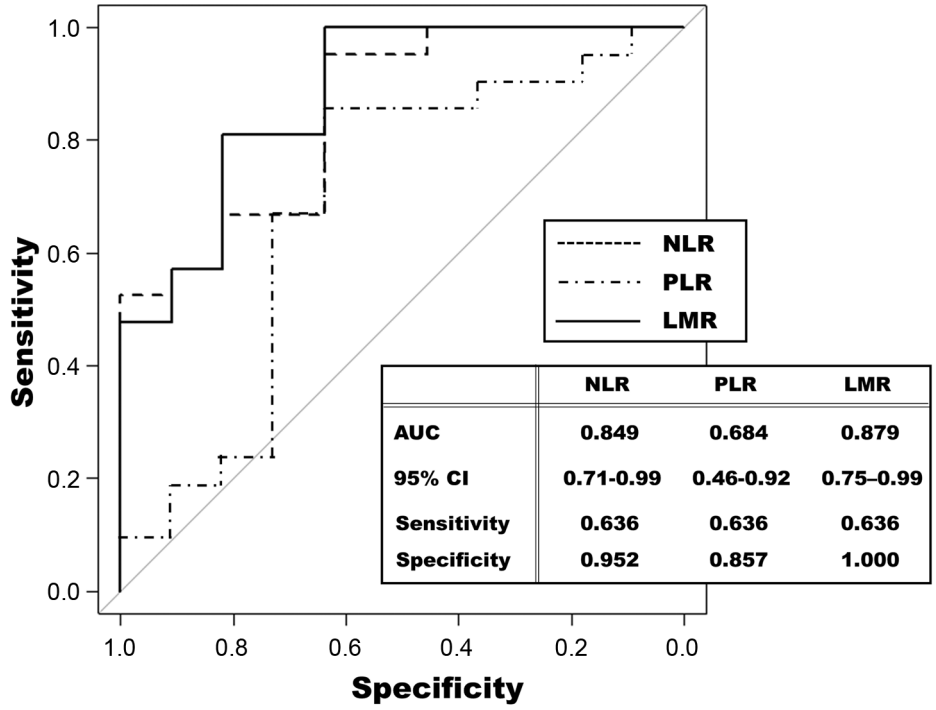

Figure 1. *Receiver operating characteristic curve analysis of inflammation-based indicators in disease control. Lymphocyte-to-monocyte ratio (LMR) showed the best predictive performance, followed by neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) [Area under the curve (AUC): 0.88, 0.85, and 0.68, respectively].*

LMR and survival. The LMR values were significantly correlated with PFS and OS (PFS: r=0.56, $p<0.001$, OS: r=0.62, $p<0.001$; Figure 2A and B). The high-LMR group showed significantly longer survival than the low group in both PFS (median: 4.9 *vs*. 2.3 m; Figure 3A) and OS (median: 21.0 *vs*. 6.1 m; Figure 3B).

Cox proportional hazards model. Exploratory analyses were performed to identify potential predictive factors for PFS and OS (Table III). In this univariate analysis, both LMR and NLR were significantly associated with PFS (LMR: $p=0.011$; NLR: $p<0.001$) and OS (LMR: $p<0.001$; NLR: $p<0.001$). PLR was significantly associated with PFS ($p<0.011$) but not with OS ($p=0.097$). In multivariate analysis (Table IV), LMR remained significantly correlated with OS (95%CI=0.26-0.79; $p=0.005$).

Discussion

In this study, LMR was the most informative marker for predicting treatment efficacy and prognosis in patients treated with TAS-102 + bevacizumab. NLR also showed a relatively good association with the tumor response, while PLR did not show a good association with OS. In multivariate analysis, only LMR, but not NLR, remained significantly correlated with OS.

Table II. *Efficacy and safety according to LMR.*

	All cases (n=32)	LMR High (≥3.18) (n=16)	LMR Low (<3.18) (n=16)	*p*-Value
CR	0 (0%)	0 (0%)	0 (0%)	
PR	2 (6.3%)	2 (12.5%)	0 (0%)	
SD	19 (59.4%)	12 (75%)	7 (43.8%)	
PD	11 (34.4%)	2 (12.5%)	9 (56.3%)	
ORR	6.3%	12.5%	0%	0.484
DCR	65.6%	87.5%	43.8%	0.023
Adverse event	(≥Grade 3)			
Leukopenia	2 (6.3%)	1 (6.3%)	1 (6.3%)	
Neutropenia	15 (46.9%)	10 (62.5%)	5 (31.3%)	
Anemia	3 (9.4%)	1 (6.3%)	2 (12.5%)	
Thrombocytopenia	4 (12.5%)	2 (12.5%)	2 (12.5%)	
Anorexia	2 (6.3%)	1 (6.3%)	1 (6.3%)	
Nausea/vomiting	2 (6.3%)	1 (6.3%)	1 (6.3%)	
Diarrhea	0 (0%)	0 (0%)	0 (0%)	
Liver dysfunction (T bil, AST, ALT)	3 (9.4%)	1 (6.3%)	2 (12.5%)	
Overall	19 (59.4%)	12 (75.0%)	9 (56.3%)	0.458

CR: Complete response; PR: partial response; LMR: lymphocyte-to-monocyte ratio; PD: progressive disease; SD: stable disease; ORR: overall response rate; DCR: disease control rate; AST: aspartate transaminase; ALT: alanine aminotransferase.

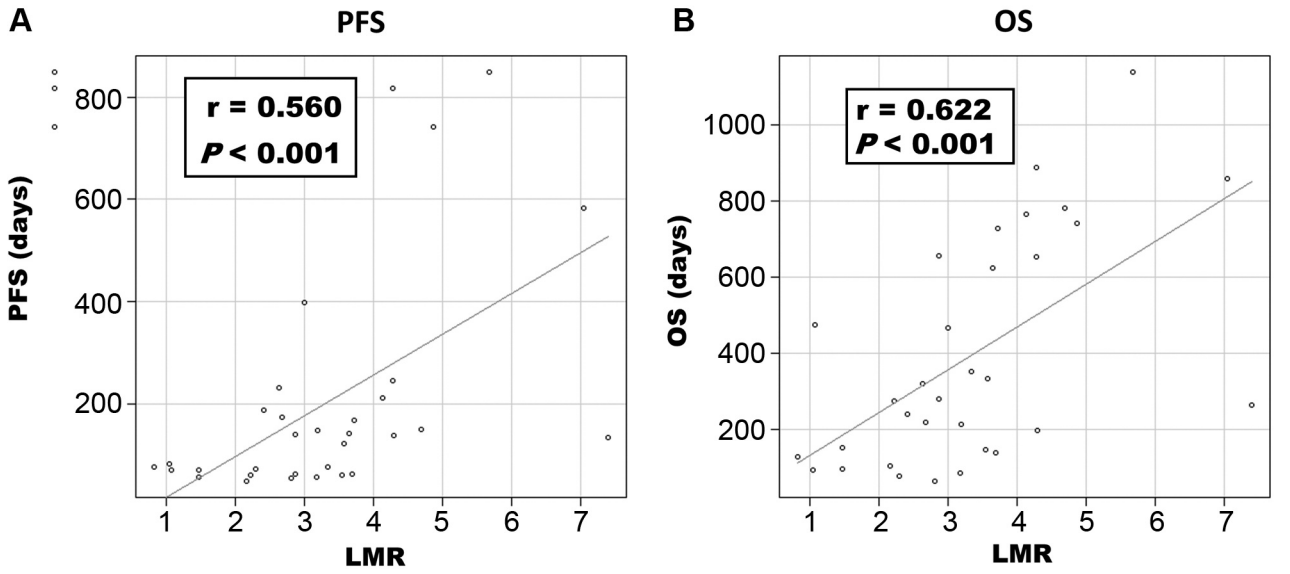

Figure 2. *Correlation between lymphocyte-to-monocyte ratio (LMR) and survival. LMR was significantly correlated with progression-free survival (PFS) (p<0.001) (A) and overall survival (OS) (p<0.001) (B).*

Table III. *PFS and OS according to prognostic factors.*

		Median PFS (months) (95%CI)	*p*-Value	Median OS (months) (95%CI)	*p*-Value
Age	<75 yrs (26)	4.6 (2.3-4.9)	0.933	9.1 (4.6-20.5)	0.943
	≥75 yrs (6)	4.3 (2.0-NA)		9.8 (4.8-NA)	
Gender	Male (20)	4.7 (2.3-7.6)	0.466	9.6 (5.1-15.6)	0.669
	Female (12)	2.5 (1.8-4.9)		9.1 (3.4-NA)	
Sidedness	Left (21)	4.6 (2.3-5.5)	0.791	11.0 (6.5-21.5)	0.428
	Right (11)	2.7 (2.0-7.0)		7.2 (3.1-15.3)	
ECOG PS	0 (23)	4.7 (2.5-5.7)	0.333	11.0 (8.0-20.5	0.136
	1 (9)	2.4 (1.8-19.1		3.2 (2.2-NA)	
RAS	Wild (14)	5.3 (2.3-8.0)	0.205	12.0 (6.5-NA)	0.266
	Mutant (18)	2.5 (2.0-4.6)		9.1 (3.4-11.6)	
Histology	tub (29)	4.6 (2.3-5.5)	0.629	9.3 (5.1-15.6)	0.789
	Por/muc (3)	4.4 (1.8-NA)		8.7 (3.2-NA)	
No. of meta sites	1 (11)	4.6 (2.0-19.1)	0.457	9.3 (3.2-NA)	0.534
	≥2 (21)	4.4 (2.3-5.7)		9.0 (5.1-15.3)	
NLR	High (16)	2.3 (1.8-2.7)	<0.001	5.8 (3.1-9.3)	<0.001
	Low (16)	5.6 (4.4-8.0)		21.0 (7.2-NA)	
PLR	High (16)	2.3 (1.8-4.6)	0.011	9.1 (4.6-15.3)	0.097
	Low (16)	5.3 (2.4-8.0)		8.9 (4.2-NA)	
LMR	High (16)	4.9 (4.0-8.0)	0.014	21.0 (7.1-NA)	<0.001
	Low (16)	2.3 (1.8-4.6)		6.1 (3.1-9.3)	

PFS: Progression-free survival; OS: overall survival; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.

NLR, LMR, and PLR are inflammatory-based markers that have been reported to be associated with patients' prognosis in various cancers. Neutrophils are the predominant leukocyte subset in human peripheral blood, with a well-established role in the first line of defense against microbial pathogens (9). Neutrophils produce serum vascular endothelial growth factor (VEGF) and various matrix proteases. This tumor-promoting microenvironment

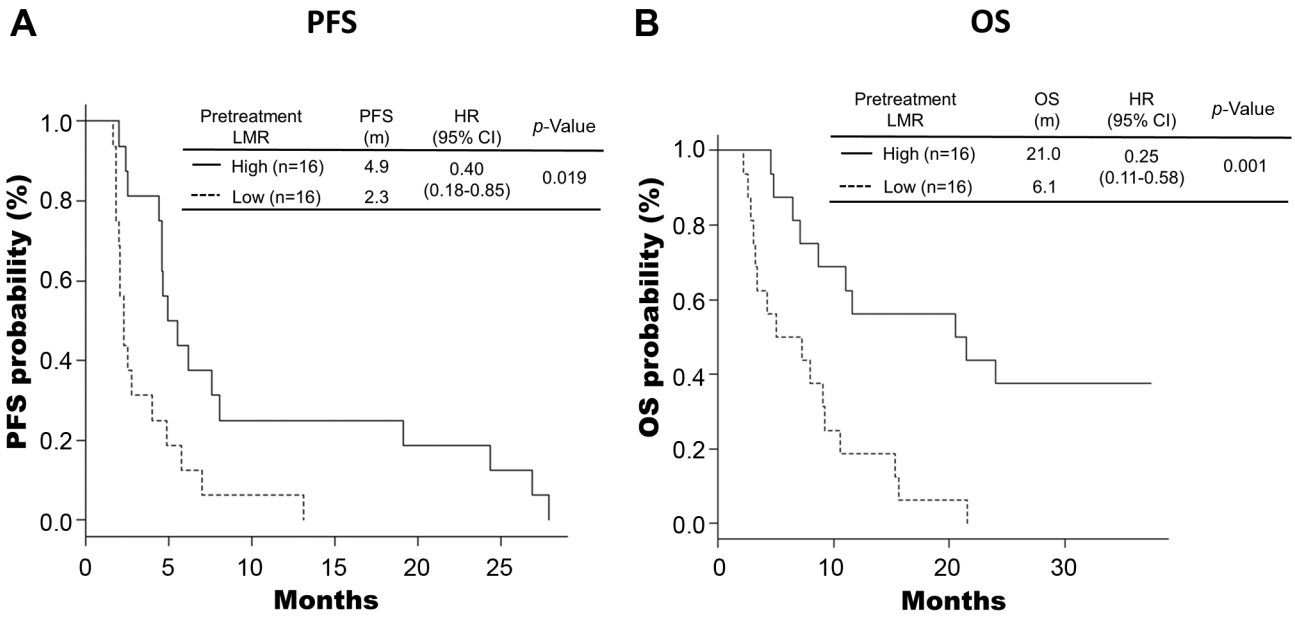

Figure 3. *Kaplan–Meier curves of progression-free survival (PFS) and overall survival (OS) according to lymphocyte-to-monocyte ratio (LMR). The high-LMR group showed significantly longer survival than the low group in both PFS (median: 4.9 vs. 2.3 m) (Figure 3A) and OS (median: 21.0 vs. 6.1 m) (Figure 3B).*

facilitates tumor invasion and metastasis (10). Thus, neutrophils are associated with cancer-related inflammation and a worse prognosis. Lymphocytes play a primary role in antitumor immunology, prohibiting tumor progression and metastasis (11). The infiltration of CD4+ T cells activates CD8+ T cells, which induce cancer cell apoptosis and exhibit cytotoxic activity toward cancer cells (12, 13). Lymphocyte depletion attenuates tumor-specific immunity, including reducing the number of tumor-infiltrating lymphocytes (14, 15). Lower pre-treatment peripheral lymphocyte counts are associated with a poor prognosis in CRC (16). Monocytes, particularly those differentiated into tumor-associated macrophages (TAMs), are involved in tumorigenesis (17). TAMs sustain tumor growth by producing growth factors (*e.g.*, EGF, VEGF, and bFGF), promote the remodeling of the extracellular matrix by releasing proteases (*e.g.*, cathepsins, MMP-2, and MMP-9) and soluble mediators (*e.g.*, TGF-beta and LL37), favorable angiogenesis and lymphangiogenesis by releasing MMP-9 or other soluble factors (*e.g.*, VEGFs, PDGF, thymidine phosphorylase, and CXCL8) and suppress the anti-tumoral immune response by releasing soluble mediators, such as IL-10, IDO and TGF-beta, as well as through a cell–cell contact mechanism (9). In CRC patients, the peripheral monocyte count was associated with a poor outcome (18, 19).

Although NLR is a well-reported index for predicting the prognosis of cancer patients, many previous studies reported the usefulness of LMR as a prognostic marker in several cancer types, such as gastric cancer (20), esophageal squamous cell cancer (21), Hodgkin's lymphoma (22), pancreatic cancer (17), and gastrointestinal stromal tumors (23). Regarding CRC, the usefulness of LMR was also reported in both curatively resected CRC patients (24-26) and mCRC patients (27, 28). Stotz *et al*. reported that the elevated preoperative LMR was significantly associated with increased time to recurrence and overall survival in stage III CRC patients (25). Chan *et al*. reported that elevated LMR was associated with better OS in retrospectively collected data from 1,623 CRC patients with curative resection (26). Shibutani *et al*. demonstrated that low pre-treatment LMR was associated with a significantly worse overall survival in mCRC patients receiving palliative

Table IV. *Multivariate analysis*.

	PFS			OS		
Variables	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
NLR	1.06	0.82-1.36	0.666	0.89	0.69-1.13	0.334
PLR	1.00	0.99-1.00	0.884			
LMR	0.67	0.44-1.01	0.056	0.45	0.26-0.79	0.005

PFS: Progression-free survival; OS: overall survival; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HR: hazard ratio; CI: confidence interval.

chemotherapy (27). Several CRC-related meta-analyses also showed consistent results (29-32).

Although the association of NLR and efficacy of chemotherapy was also demonstrated in this study, the association of NLR with OS was weaker than that of LMR. Only 3rd-line mCRC patients were included in this study, therefore, the pre-treatment blood data were affected by previous chemotherapy. Shibutani *et al*. determined the pre-treatment and post-treatment absolute neutrophil/lymphocyte/monocyte counts in 104 patients with unresectable mCRC who had undergone palliative chemotherapy (27). According to these data, the neutrophil counts were highly decreased and the monocyte counts were slightly elevated, however, the lymphocyte counts were not strongly affected after chemotherapy. Thus, in this late-line setting, NLR was affected by previous chemotherapy and was decreased, inaccurately indicating a better prognosis. Although LMR was elevated, the difference in the monocyte counts pre- and post-chemotherapy was smaller than the change in the neutrophil count. Therefore, NLR in this late-line setting cannot predict a precise prognosis, likely because of the influence of previous chemotherapy.

There are some limitations in this study. First, the number of included patients was relatively small. Second, the median values of each marker were used as cut-off values to divide the high and low groups, while the appropriate cut-off value to show the best segregation was not determined. Third, we did not specify 4th-line chemotherapy; thus, we cannot discount the possibility that OS was influenced by the type of 4th-line chemotherapy.

In conclusion, our study indicated that pre-treatment LMR is a valid predictive and prognostic biomarker for mCRC patients treated with TAS-102 and bevacizumab and may be clinically useful for selecting responder patients.

Conflicts of Interest

H.Kuramochi received scholarship donation from Chugai pharmaceuticals, Ltd. and Taiho Pharmaceutical Co, Ltd. H.Ishida received research funding from Chugai pharmaceuticals, Ltd. and Taiho Pharmaceutical Co, Ltd.

Authors' Contributions

HK participated in the clinical trial and drafted the manuscript. TY designed this clinical trial and helped editing the manuscript. AM performed the statistical analysis. YY, HiK, CK, KI, AF, KI, HS, KY, HY, SH, KS, HI, and KK participated in this clinical trial. All Authors read and approved the final manuscript.

Acknowledgements

The Authors thank all the patients and co-workers for their participation and cooperation in the TAS-CC3 study. The Authors also thank Nicole Okoh, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

Funding

All the treatments in this study were covered by national health insurance. There are no competing interests between pharmaceutical companies and the investigators regarding this study that require disclosure.

Trial Registration Information

Registry name: TAS-102 and Bevacizumab as third-line chemotherapy for colorectal cancer. Phase 2 trial (TAS-CC3 study). Trial ID: UMIN000022438. URL: https://upload.umin.ac.jp/cgi-open-in/ctr/ctr_view.cgi?recptno=R000025861

References

1 Emura T, Murakami Y, Nakagawa F, Fukushima M and Kitazato K: A novel antimetabolite, TAS-102 retains its effect on FU-related resistant cancer cells. Int J Mol Med *13(4)*: 545-549, 2004. PMID: 15010854.

2 Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A and RECOURSE Study Group: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med *372(20)*: 1909-1919, 2015. PMID: 25970050. DOI: 10.1056/NEJMoa1414325

3 Kuboki Y, Nishina T, Shinozaki E, Yamazaki K, Shitara K, Okamoto W, Kajiwara T, Matsumoto T, Tsushima T, Mochizuki N, Nomura S, Doi T, Sato A, Ohtsu A and Yoshino T: TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. Lancet Oncol *18(9)*: 1172-1181, 2017. PMID: 28760399. DOI: 10.1016/S1470-2045(17)30425-4

4 Yoshida Y, Yamada T, Kamiyama H, Kosugi C, Ishibashi K, Yoshida H, Ishida H, Yamaguchi S, Kuramochi H, Fukazawa A, Sonoda H, Yoshimatsu K, Matsuda A, Hasegawa S, Sakamoto K, Otsuka T, Koda K and TAS CC3 Study Group: Combination of TAS-102 and bevacizumab as third-line treatment for metastatic colorectal cancer: TAS-CC3 study. Int J Clin Oncol *26(1)*: 111-117, 2021. PMID: 33083913. DOI: 10.1007/s10147-020-01794-8

5 Satake H, Kato T, Oba K, Kotaka M, Kagawa Y, Yasui H, Nakamura M, Watanabe T, Matsumoto T, Kii T, Terazawa T, Makiyama A, Takano N, Yokota M, Okita Y, Matoba K, Hasegawa H, Tsuji A, Komatsu Y, Yoshino T, Yamazaki K, Mishima H, Oki E, Nagata N and Sakamoto J: Phase Ib/II study of biweekly TAS-102 in combination with bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (BiTS Study). Oncologist *25(12)*: e1855-e1863, 2020. PMID: 32666647. DOI: 10.1634/theoncologist.2020-0643

6 Yoshida Y, Yamada T, Matsuoka H, Hirata K, Kuramochi H, Kosugi C, Takahashi M, Fukazawa A, Sonoda H, Matsuda A, Watanabe T, Koizumi M, Aisu N, Hasegawa S, Yoshida H, Sakamoto K, Ishida H and Koda K: Biweekly TAS-102 and bevacizumab as a third-line chemotherapy for metastatic colorectal cancer: A phase II multicenter clinical trial (TAS-CC4 study). Annals of Oncology *30*: v235, 2020. DOI: 10.1093/annonc/mdz246.098

7 Pfeiffer P, Yilmaz M, Möller S, Zitnjak D, Krogh M, Petersen LN, Poulsen LØ, Winther SB, Thomsen KG and Qvortrup C: TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. Lancet Oncol *21(3)*: 412-420, 2020. PMID: 31999946. DOI: 10.1016/S1470-2045(19)30827-7

8 Matsuda A, Yamada T, Matsumoto S, Sakurazawa N, Kawano Y, Shinozuka E, Sekiguchi K, Suzuki H and Yoshida H: Pretreatment neutrophil-to-lymphocyte ratio predicts survival after tas-102 treatment of patients with metastatic colorectal cancer. Anticancer Res *39(8)*: 4343-4350, 2019. PMID: 31366528. DOI: 10.21873/anticanres.13602

9 Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A and Jaillon S: Tumor associated macrophages and neutrophils in cancer. Immunobiology *218(11)*: 1402-1410, 2013. PMID: 23891329. DOI: 10.1016/j.imbio.2013.06.003

10 Balkwill F and Mantovani A: Inflammation and cancer: back to Virchow? Lancet *357(9255)*: 539-545, 2001. PMID: 11229684. DOI: 10.1016/S0140-6736(00)04046-0

11 Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature *454(7203)*: 436-444, 2008. PMID: 18650914. DOI: 10.1038/nature07205

12 Zikos TA, Donnenberg AD, Landreneau RJ, Luketich JD and Donnenberg VS: Lung T-cell subset composition at the time of surgical resection is a prognostic indicator in non-small cell lung cancer. Cancer Immunol Immunother *60(6)*: 819-827, 2011. PMID: 21373990. DOI: 10.1007/s00262-011-0996-4

13 Rosenberg SA: Progress in human tumour immunology and immunotherapy. Nature *411(6835)*: 380-384, 2001. PMID: 11357146. DOI: 10.1038/35077246

14 Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, Chang GJ, Qiao W, Morris J, Hong D, Hoff P, Tran H, Menter DG, Heymach J, Overman M and Kopetz S: Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer *112(6)*: 1088-1097, 2015. PMID: 25688736. DOI: 10.1038/bjc.2015.61

15 Coussens LM and Werb Z: Inflammation and cancer. Nature *420(6917)*: 860-867, 2002. PMID: 12490959. DOI: 10.1038/nature01322

16 Kim US, Papatestas AE and Aufses AH Jr: Prognostic significance of peripheral lymphocyte counts and carcinoembryonic antigens in colorectal carcinoma. J Surg Oncol *8(3)*: 257-262, 1976. PMID: 933547. DOI: 10.1002/jso.2930080312

17 Hu RJ, Ma JY and Hu G: Lymphocyte-to-monocyte ratio in pancreatic cancer: Prognostic significance and meta-analysis. Clin Chim Acta *481*: 142-146, 2018. PMID: 29544747. DOI: 10.1016/j.cca.2018.03.008

18 Sasaki A, Kai S, Endo Y, Iwaki K, Uchida H, Tominaga M, Okunaga R, Shibata K, Ohta M and Kitano S: Prognostic value of preoperative peripheral blood monocyte count in patients with colorectal liver metastasis after liver resection. J Gastrointest Surg *11(5)*: 596-602, 2007. PMID: 17468918. DOI: 10.1007/s11605-007-0140-0

19 Hu S, Zou Z, Li H, Zou G, Li Z, Xu J, Wang L and Du X: The preoperative peripheral blood monocyte count is associated with liver metastasis and overall survival in colorectal cancer patients. PLoS One *11(6)*: e0157486, 2016. PMID: 27355390. DOI: 10.1371/journal.pone.0157486

20 Ma J and Liu Q: Clinicopathological and prognostic significance of lymphocyte to monocyte ratio in patients with gastric cancer: A meta-analysis. International Journal of Surgery *50*: 67-71, 2020. DOI: 10.1016/j.ijsu.2018.01.002

21 Hu G, Liu G, Ma JY and Hu RJ: Lymphocyte-to-monocyte ratio in esophageal squamous cell carcinoma prognosis. Clin Chim Acta *486*: 44-48, 2018. PMID: 30028962. DOI: 10.1016/j.cca.2018.07.029

22 Koh YW, Kang HJ, Park C, Yoon DH, Kim S, Suh C, Go H, Kim JE, Kim CW and Huh J: The ratio of the absolute lymphocyte count to the absolute monocyte count is associated with prognosis in Hodgkin's lymphoma: correlation with tumor-associated macrophages. Oncologist *17(6)*: 871-880, 2012. PMID: 22588324. DOI: 10.1634/theoncologist.2012-0034

23 Cananzi FCM, Minerva EM, Samà L, Ruspi L, Sicoli F, Conti L, Fumagalli Romario U and Quagliuolo VL: Preoperative monocyte-to-lymphocyte ratio predicts recurrence in gastrointestinal stromal tumors. J Surg Oncol *119(1)*: 12-20, 2019. PMID: 30426498. DOI: 10.1002/jso.25290

24 Shimura T, Shibata M, Gonda K, Hayase S, Sakamoto W, Okayama H, Fujita S, Saito M, Momma T, Ohki S and Kono K: Prognostic impact of preoperative lymphocyte-to-monocyte ratio in patients with colorectal cancer with special reference to myeloid-derived suppressor cells. Fukushima J Med Sci *64(2)*: 64-72, 2018. PMID: 30012939. DOI: 10.5387/fms.2018-10

25 Stotz M, Pichler M, Absenger G, Szkandera J, Arminger F, Schaberl-Moser R, Samonigg H, Stojakovic T and Gerger A: The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer *110(2)*: 435-440, 2014. PMID: 24357796. DOI: 10.1038/bjc.2013.785

26 Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A and Clarke SJ: The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg *265(3)*: 539-546, 2017. PMID: 27070934. DOI: 10.1097/SLA.0000000000001743

27 Shibutani M: Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer. World Journal of Gastroenterology *21(34)*: 9966, 2019. DOI: 10.3748/wjg.v21.i34.9966

28 Facciorusso A, Del Prete V, Crucinio N, Serviddio G, Vendemiale G and Muscatiello N: Lymphocyte-to-monocyte ratio predicts survival after radiofrequency ablation for colorectal liver metastases. World J Gastroenterol *22(16)*: 4211-4218, 2016. PMID: 27122671. DOI: 10.3748/wjg.v22.i16.4211

29 Tan D, Fu Y, Tong W and Li F: Prognostic significance of lymphocyte to monocyte ratio in colorectal cancer: A meta-analysis. Int J Surg *55*: 128-138, 2018. PMID: 29807167. DOI: 10.1016/j.ijsu.2018.05.030

30 Wu Q, Hu T, Zheng E, Deng X and Wang Z: Prognostic role of the lymphocyte-to-monocyte ratio in colorectal cancer: An up-to-date meta-analysis. Medicine (Baltimore) *96(22)*: e7051, 2017. PMID: 28562566. DOI: 10.1097/MD.0000000000007051

31 Song W, Wang K, Zhang RJ and Zou SB: Prognostic value of the lymphocyte monocyte ratio in patients with colorectal cancer: A meta-analysis. Medicine (Baltimore) *95(49)*: e5540, 2016. PMID: 27930549. DOI: 10.1097/MD.0000000000005540

32 Guo YH, Sun HF, Zhang YB, Liao ZJ, Zhao L, Cui J, Wu T, Lu JR, Nan KJ and Wang SH: The clinical use of the platelet/lymphocyte ratio and lymphocyte/monocyte ratio as prognostic predictors in colorectal cancer: a meta-analysis. Oncotarget *8(12)*: 20011-20024, 2017. PMID: 28212553. DOI: 10.18632/oncotarget.15311

Received April 8, 2021
Revised April 20, 2021
Accepted April 21, 2021