Neutrophil-related Variables Have Different Prognostic Effect Based on Primary Tumor Location in Patients With Metastatic Colorectal Cancer Receiving Chemotherapy

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Abstract

In contrast with patients with other advanced tumors, the relationship among systemic inflammation-related variables and prognosis is controversial among patients with metastatic colorectal cancer. In this retrospective analysis of 145 patients with metastatic colorectal cancer, we found that neutrophil-related variables predicted overall survival for patients with left-sided tumors and not for those with a right-sided cancer.

Background: Clinical data reported a relationship between neutrophil-related variables and poor prognosis in patients with metastatic colorectal cancer (mCRC), but only platelet-to-lymphocyte ratio has been reported as prognostic. **Patients and Methods:** A retrospective analysis of 145 patients with mCRC, who received chemotherapy at the department of Oncology of the Ospedale Civile di Sanremo in 2010 to 2013, was performed, and a Cox model was built. **Results:** In the model, some variables were independently related with overall survival (OS) (resection of the primary tumor, number of drugs included in the first-line chemotherapy regimen), whereas neutrophil-related ones were not. However, after stratification by tumor location, neutrophil-related variables appeared associated with a poor survival among patients with a left-sided mCRC, and in particular, among those ones with a rectal tumor (hazard ratio, 3.732; 95% confidence interval, 1.575-8.845). **Conclusion:** Neutrophil-related variables predicted outcome in patients with left-sided mCRC only. A high prevalence of consensus molecular subtype 4 CRC in patients with metastatic cancer of the rectum is suggested.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death among men and the third among women in the European Union.[1] About 15% to 25% of patients with CRC are diagnosed with synchronous metastases, and another 10% to 20% develop metastases later.[2] A meta-analysis of 13 prospective trials concluded that the primary tumor localization along the colon is prognostic in metastatic colorectal cancer (mCRC), and was associated with a different activity of anti-neoplastic drugs.[3]

Systemic inflammation response (SIR) in CRC can play dual roles, contributing to anti-neoplastic response or promoting tumor cell proliferation and metastasis.[4] Data from controlled clinical trials and retrospective studies reported a significant relationship between neutrophil-to-lymphocyte ratio (NLR) or derived neutrophil-to-lymphocyte ratio (dNLR) and outcome of patients with mCRC.[5-9] Although inflammation plays a role in the development of metastases, many studies have not confirmed the relationship between NLR and overall survival (OS) in mCRC. Recently, however, one of these studies has reported a significant relationship between the platelet-to-lymphocyte ratio (PLR) and OS only among patients with left-sided mCRC.[10] Finally, the neutrophil platelet score (NPS) has been studied in 308 patients with localized CRC, and this study concluded that NPS was able to predict prognosis within each stage of disease.[11] In patients with other metastatic neoplasms, NPS was superior to NLR,[12] but no data about NPS in mCRC are available.

The purpose of this study is to verify whether the neutrophil-related variables predict the outcome of patients with mCRC receiving a first-line chemotherapy (CHT), and whether there are differences by tumor location.

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Patients and Methods

Patients and Treatments

Data of patients with a diagnosis of mCRC, registered in the database of the division of Medical Oncology of the Ospedale Civile di Sanremo, were analyzed, and those patients who received at least 1 cycle of first-line CHT between January 2010 and January 2013 were collected. Patients were included in the present analysis if they were diagnosed with TNM stage IV or a relapse of the CRC, had a censoring, and have signed an informed consent form. All the results of the complete blood counts carried out at the beginning of the first cycle of CHT were collected. The determinations of cell blood counts were performed at the Laboratorio Analisi department of the Ospedale Civile di Sanremo.

OS was defined as the time from the starting date of CHT until death from any cause.

A series of 22 variables were extracted for each patient form the clinical records at the time of initiation of first-line CHT, such as Eastern Cooperative Oncology Group performance status (ECOG PS), gender, age, body mass index (BMI), height, number of comorbidities, family history of CRC, tumor location, stage at diagnosis, timing of metastases, previous resection of primary tumor, baseline serum carcinoembryonic antigen (CEA), baseline serum carbohydrate antigen 19-9 (CA 19-9), number of drugs included in the first-line CHT regimen, number of metastatic sites, nodal metastases, lung metastases, peritoneal metastases, liver metastases, and finally, the neutrophil count, dNLR, and NPS. Tumor location was identified by the International Classification of Diseases: cases with a neoplasm of cecum, ascending colon, hepatic flexure, and transverse were reported as having a right-sided tumor, those with a neoplasm of splenic flexure, descending colon, sigmoid, and sigmoid-rectal junction were classified as having a left-sided one, and finally, those with a rectal tumor were reported separately. Family history for CRC was ascertained by history-taking during the first 2 accesses of the patient to the department, considering the American Society of Clinical Oncology (ASCO) recommendations regarding the minimum adequate family history for patients with cancer. CEA and CA 19-9 were measured at the time of the beginning of first-line CHT. Baseline neutrophil count, NLR, and dNLR were calculated and were examined as continuous. NPS was calculated by the baseline blood count, and cutoff values for defining the score were the upper limits of the normal range of the Laboratorio Analisi of the Ospedale Civile di Sanremo, which were 7000/microliter for neutrophils and 400,000/microliter for platelets: if one or both neutrophils and platelets were higher than these upper limits, the score was 1 or 2, respectively. OS was calculated from the start of first-line CHT until death by any cause or was censored at the last follow-up visit.

Statistical Analysis

A preliminary analysis of the distribution of the variables was performed by the Kolmogorov-Smirnov test. Whenever a normal distribution was not verified, a transformation of the scale or the exclusion of the variable from further analyses were considered.

OS was estimated using the Kaplan-Meier method. A bivariate analysis between the variables and OS defined those that were suitable to be included in a multivariate Cox model. All those variables that were statistically associated with OS were tested via multivariate analysis, building a Cox model with the aim of identifying the most important prognostic factors. Further exploratory analyses were done among the subgroups of the patients with previous resection of the primary tumor or not, and by tumor location (right vs. left colon vs. rectum). The hazard ratio (HR) and 95% confidence intervals (CIs) were calculated by Cox regression models, and a 2-tailed P-value $< .05$ was considered statistically significant.

All statistical analyses were conducted with the statistical computing language R (version 3.4.1 for Linux).

Results

Of 145 screened patents with mCRC receiving CHT, 140 received at least 1 complete cycle of first-line CHT and were eligible by the criteria of the current analysis. The characteristics of the 140 selected patients are reported in Table 1.

The median OS was 19.8 months (range, 2.2-106.9 months). NLR was available for 88 patients, and there was a high level of collinearity with dNLR (Pearson rho = 0.916; P-value $< .001$), thus NLR was excluded from the further analyses. After controlling for the distribution of variables, 4 were retained with their scale transformation into logarithmic (CEA, neutrophil count, dNLR, OS), and one (CA 19-9) was excluded owing to its not-normal distribution even after transformation.

Tables 2 and 3 lists the results of the bivariate analyses for each of the variables (Table 2) and those of the neutrophil-related variables by sidedness (Table 3). After bivariate analysis, 9 variables were associated with OS, but 2 (neutrophil count and dNLR) were excluded owing to their collinearity with NPS (rho, 0.578 and 0.645, respectively), which was retained for multivariate analysis.

As a result, a Cox model was constructed comprising 6 variables, which were ECOG PS, presence of the primary tumor, baseline CEA, number of sites of metastases, number of drugs in the first-line regimen, and NPS (Table 4). The model reported a negative effect of the presence of the primary tumor on OS (HR, 3.467; 95% CI, 1.952-6.158), and a positive effect of a higher number of drugs in the CHT regimen (HR, 0.527; 95% CI, 0.382-0.728), which were confirmed in the 2 subgroups with the primary tumor removed (116 patients) or not (24 patients), as listed in Table 5. After stratification by tumor side (Table 6), it appeared that the Cox model reported similar results for both the variables (presence of primary tumor, number of drugs), but different results for NPS in patients with metastatic right-sided CRC (HR, 0.663; 95% CI, 0.345-1.275) versus left-sided tumors (HR, 1.107; 95% CI, 0.653-1.878) versus rectal cancer (HR, 3.732; 95% CI, 1.575-8.845).

Discussion

The conclusion of the present study about the neutrophil-related variables in patients with mCRC receiving CHT is that an independent relationship with OS is evident for rectal tumors, whereas neutrophil-related variables have no prognostic role in right-sided and left-sided CRC. To date, this location-related difference has been demonstrated only for PLR,[10] and not for the neutrophil count, the dNLR, or NPS. Although the prognostic relevance of tumor location along the colon-rectum is not fully explained by other variables, there is some indirect evidence to

Table 1 Characteristics of Patients (n = 140)

Variable	N
Age, y	
Median (range)	70 (44-85)
Gender	
Male	76
Female	64
Stage at diagnosis	
I-II	25
III	40
IV	75
Sidedness	
Right	37
Left	103
Primary tumor	
Resected	116
Not resected	24
ECOG PS	
0	106
1	29
2	5
Metastatic site	
Loco-regional	29
Liver	95
Lung	45
Nodes	36
Peritoneum	25
Bone	9
Other sites	7
Comorbid conditions	
0	20
1	34
2	45
>2	41
Baseline CEA, nanograms/mL	
Median (range)	17.5 (0.8-12075.0)
Baseline CA 19-9, units/mL	
Median (range)	37.7 (0.6-23090.0)
NLR	
Median (range)	3.05 (1.07-14.28)
dNLR	
Median (range)	1.95 (0.41-15.28)
PLR	
Median (range)	176.8 (59.8-671.7)

Abbreviations: CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; dNLR = derived neutrophil to lymphocyte ratio; ECOG PS = Eastern Cooperative Oncology Group performance status; NLR = neutrophil to lymphocyte ratio; PLT = platelet to lymphocyte ratio.

support a different behavior of neutrophil-related variables within different CRC subgroups. Specifically, 2 studies have documented that NLR has a prognostic effect in cases with mismatch repair (MMR) proficient tumors, but a distinction by tumor location was not made.[13,14]

Table 2 Bivariate Analyses of Each Potential Prognostic Variable (Each Variable With Overall Survival)

Variable	No. Patients	HR	95% CI	*P* Value
ECOG PS (higher vs. lower)	140	1.659	1.202-2.290	.002
Gender (male vs. female)	140	1.158	0.825-1.625	.397
Age (younger vs. older)	140	1.021	0.999-1.043	.057
BMI (lower vs. higher)	140	0.970	0.930-1.013	.168
Altezza (lower vs. higher)	140	0.466	0.060-3.588	.463
No. comorbid conditions (lower vs. higher)	140	1.035	0.928-1.154	.537
Family history (negative vs. positive)	104	0.814	0.505-1.311	.397
Tumor side (left vs. right)	140	0.770	0.523-1.133	.184
Stage at diagnosis (IV vs. I-III)	140	1.201	0.985-1.465	.071
Timing (metachronous vs. synchronous)	140	0.746	0.527-1.055	.098
Primary tumor (removed vs. present)	140	5.268	3.222-8.614	<.001
Baseline CEA (higher vs. lower)	137	1.131	1.043-1.226	.003
Baseline CA 19-9 (higher vs. lower)	131	1.182	1.073-1.303	.001
No. drugs first-line (higher vs. lower)	140	0.514	0.377-0.701	<.001
No. sites of metastases (high vs. low)	140	1.436	1.161-1.775	.001
Lymph node metastases (yes vs. no)	140	1.319	0.897-1.940	.160
Lung metastases (yes vs. no)	140	0.796	0.553-1.146	.220
Peritoneal metastases (yes vs. no)	140	1.543	0.993-2.398	.054
Liver metastases (yes vs. no)	140	1.343	0.934-1.932	.112
Neutrophil count (high vs. low)	140	1.688	1.051-2.711	.030
dNLR (high vs. low)	140	1.559	1.103-2.203	.012
NPS (high vs. low)	140	1.743	1.317-2.306	<.001

In the study sample, median OS on the basis of the tumor location was numerically different (right-sided, 17.5 months; left-sided, 20.5 months; rectum, 22.7 months) although the difference was not significant (log-rank test, 1.846; *P*-value = .397; data not shown). Despite this better prognosis of patients with rectal neoplasms, the study identified a subgroup of patients with rectal

Table 3 Bivariate Analyses of Neutrophil-Related Variables (Each Variable With Overall Survival)

Variable	No. Patients	HR	95% CI	*P* Value
Neutrophil count (high vs. low)				
Right-sided	37	1.014	0.371-2.774	.979
Left-sided	62	2.361	1.108-5.030	.026
Rectum	41	1.585	0.644-3.901	.316
dNLR (high vs. low)				
Right-sided	37	1.889	0.805-4.429	.144
Left-sided	62	1.275	0.811-2.005	.292
Rectum	41	2.787	1.152-6.740	.023
NPS (high vs. low)				
Right-sided	37	1.306	0.811-2.105	.272
Left-sided	62	1.785	1.148-2.776	.010
Rectum	41	3.666	1.769-7.597	<.001

Abbreviations: BMI = body mass index; CA 19-9 = carbohydrate antigen 19-9; CI = confidence interval; dNLR = derived neutrophil to lymphocyte ratio; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NPS = neutrophil platelet score.

tumors with SIR activation and poor prognosis, similar to what was reported by other authors.[10,15]

Inflammation helps to support a tumor microenvironment that favors invasion and metastasis, a microenvironment whose immune cells produce various cytokines and signals that influence tumor cells and stromal cells.[16] As part of this complex system of interactions between different cell populations in the tumor stroma, analogously to platelets, neutrophils can also contribute to promote metastasis, as evidenced by the correspondence in many solid neoplasms between the high number of neutrophils in the peripheral blood and the increased risk of distant metastases.[17] Unfortunately, to date, it is not possible to draw definitive conclusions on these relationships, because even a recent study has documented at least 22 different types of immune cells within the CRC infiltrates,[18] not to mention

Table 4 Cox Proportional Hazard Model: Model Including the Baseline Variables That Were Associated With OS in Bivariate Analysis

Variable	No. Patients	HR	95% CI	*P* Value
ECOG PS (high vs. low)	137	1.187	0.844-1.669	.324
Primary tumor (removed vs. present)	137	3.467	1.952-6.158	<.001
Baseline CEA (high vs. low)	137	1.041	0.947-1.145	.404
No. sites of metastases (high vs. low)	137	1.250	0.992-1.574	.058
No. drugs CHT (high vs. low)	137	0.527	0.382-0.728	<.001
NPS (high vs. low)	137	1.186	0.837-1.610	.276

Table 5 Model Including the Baseline Variables in the Group With and Without Primary Tumor Resection

Variable	No. Patients	HR	95% CI	*P* Value
Primary tumor resected				
ECOG PS (higher vs. lower)	113	1.103	0.722-1.684	.650
Baseline CEA (higher vs. lower)	113	1.064	0.959-1.180	.244
No. sites of metastases (high vs. low)	113	1.306	1.007-1.693	.044
No. drugs CHT (high vs. low)	113	0.577	0.401-0.829	.003
NPS (high vs. low)	113	1.286	0.879-1.882	.196
Primary tumor not resected				
ECOG PS (higher vs. lower)	24	1.108	0.597-2.057	.744
Baseline CEA (higher vs. lower)	24	0.931	0.731-1.186	.562
No. sites of metastases (high vs. low)	24	1.058	0.549-2.037	.867
No. drugs CHT (high vs. low)	24	0.300	0.106-0.852	.024
NPS (high vs. low)	24	1.543	0.687-3.463	.293

Abbreviations: CEA = carcinoembryonic antigen; CHT = systemic chemotherapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NPS = neutrophil platelet score.

the complex relationships between cells of the lymphoid and monocyte-macrophagic lines and the neoplastic stroma within the different molecular subtypes of CRC. However, current evidence suggests that neutrophil tumor infiltration remains a negative prognostic event.[19]

In 2015, a consortium reported a molecular classification of CRCs in 4 subtypes, defined as consensus molecular subtypes (CMS).[20] Within the various CMS, gene expressions revealed an excess of lymphoid-specific and myeloid-specific genes involved in inflammation for 2 subtypes, CMS1 and CMS4.[21] Although CMS4 is the subtype with the worst prognosis and is characterized by a frequent expression of an inflammatory phenotype (stromal invasion, poor immune infiltrates, high tumor-stromal percentage, epithelial mesenchymal transition, high levels of TGF-beta and VEGF), it does not present a differential distribution along the colon-rectum.[22] In our sample of patients with mCRC, the rectal location suggests a greater involvement of SIR; therefore, in the context of mCRC, CMS4 could be more frequent at the rectal site, even though we cannot exclude that our result could rather be attributable to the CMS2 subtype,[10] which is more frequent at the rectum, and for which an activation of the inflammatory pathways and a predominantly immunosuppressive microenvironment have also been described.[23,24]

Although we consider it inappropriate to argue for an "inflammatory phenotype" only for the presence of 1 or more increased scores or ratios, as suggested by some authors,[25] the correlation of

Table 6 Cox Proportional Hazard Model by Tumor Sidedness

Variable	No. Patients	HR	95% CI	*P* Value
Right-sided tumors				
ECOG PS (high vs. low)	37	0.737	0.308-1.764	.493
Primary tumor (removed vs. present)	37	18.253	2.678-124.419	.003
Baseline CEA (high vs. low)	37	0.988	0.756-1.293	.932
No. sites of metastases (high vs. low)	37	1.199	0.783-1.835	.404
No. drugs CHT (high vs. low)	37	0.305	0.116-0.799	.016
NPS (high vs. low)	37	0.663	0.345-1.275	.218
Left-sided tumors				
ECOG PS (high vs. low)	62	2.088	1.060-4.113	.033
Primary tumor (removed vs. present)	62	3.161	1.104-9.051	.032
Baseline CEA (high vs. low)	62	1.016	0.884-1.166	.827
No. sites of metastases (high vs. low)	62	1.115	0.780-1.595	.549
No. drugs CHT (high vs. low)	62	0.601	0.390-0.924	.020
NPS (high vs. low)	62	1.107	0.653-1.878	.705
Rectal tumors				
ECOG PS (high vs. low)	41	0.580	0.291-1.157	.122
Primary tumor (removed vs. present)	41	2.973	0.952-9.283	.061
Baseline CEA (high vs. low)	41	0.993	0.815-1.211	.948
No. sites of metastases (high vs. low)	41	1.907	1.075-3.382	.027
No. drugs CHT (high vs. low)	41	0.389	0.166-0.907	.029
NPS (high vs. low)	41	3.732	1.575-8.845	.003

Abbreviations: CEA = carcinoembryonic antigen; CHT = systemic chemotherapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NPS = neutrophil platelet score.

the neutrophil count with OS has been demonstrated in patients with mCRC.[26] As previously reported, similar evidence exists for NLR from clinical trials[5,6] and case series.[7,8,27] Although remembering that the association with prognosis is limited to cases with proficient MMR,[13,14] no correlation of NLR was found with any of the biological characteristics of CRC, but rather with a complex network of at least 20 cytokines.[8] These data, in our opinion, are a further confirmation of the prognostic role of NLR in patients with left-sided tumors. Among the studies about the PLR in mCRC, the study that reported that the PLR was prognostic in left-sided tumors unfortunately did not distinguish the patients with rectal mCRC from those with left-sided mCRC,[10] similar to other studies that have confirmed a prognostic role for PLR.[27,28] However, after a comprehensive analysis of clinical and preclinical data, some authors have reported an interesting high number of evidence on the possible relationship between the role of platelets and the inflammatory phenotype with the CMS4 subtype of CRC.[29] Given a most recent introduction of the second-generation combined scores, a limited number of studies are available for COP-NLR[30] and NPS[11] in patients with CRC, whereas there are no published experiences in patients with mCRC. We can therefore conclude by hypothesizing that the involvement of SIR with a tumor-favoring effect among patients with a metastatic rectal tumor is probably attributed to a more frequent occurrence of some molecular subtypes among these patients, in particular the CMS4.

In this complex interplay of SIR regulation, the presence of the primary tumor has an important role, as shown by the results reported in Tables 4 and 5, and its clinical relevance has still to be completely clarified. A recent meta-analysis of 21 studies (44,000 patients) of patients with unresectable mCRC has documented a better OS for patients with a previous primary tumor resection (odds ratio [OR], 0.28; 95% CI, 0.16-0.47).[31] These results have been confirmed by prospective cohorts,[32,33] but there is no evidence from randomized trials. The importance of resection of the primary tumor compared with the site of the CRC is not well-known, but the impact on OS of the reversal of NLR after the resection of the primary tumor is well-known[34]; therefore, we can infer that it could be more important in left-sided and rectal tumors. The limited numbers do not allow us further conclusions, but among the 24 patients who had not received a primary tumor resection, the median OS appears lower than that of the 116 patients with a primary tumor resection (8.4 vs. 21.6 months), with a similar effect at any location, in patients with rectal tumors (9 vs. 32; median OS, 7.6 vs. 24.3 months) and with right-sided CRC (5 vs. 32; median OS, 4.7 vs. 19.5 months).

The limits of the present analysis are many. First, there is the retrospective character of the study, but also the lack of data on the peripheral lymphocyte count in many clinical records, and on the molecular characteristics of tumors such as RAS, BRAF, and MMR. In addition, we decided to maintain a 2-sided cutoff of 0.05 for *P*-values because, after the bivariate analyses, the number of variables selected for the multivariate analyses was limited.

Despite all the limitations of the study, the data allow us to draw an important conclusion regarding the possible role of SIR in the carcinogenesis of mCRC, suggesting the involvement of the inflammation pathways only in the most distal mCRCs, and probably within the CMS4 subtype. Therefore, the prognostic role

of inflammatory markers should be reassessed based on the location of the primary tumor and may be indicative of the molecular subtype. Future studies of confirmation of our results and of correlation with the CMS are strongly recommended.

Clinical Practice Points

- To date, neutrophil-related variables have displayed controversial results among patients with mCRC.
- Only one study reported a different relationship of PLR with a poor prognosis in left-sided versus right-sided colorectal tumors.
- In the present analysis, a relationship of neutrophil-related variables with the outcome has been reported for left-sided tumors only, whereas it was not significant for right-sided tumors.
- A possible role for systemic inflammation is suggested for left-sided CMS4 colorectal tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

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