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The Neutrophil-to-lymphocyte Ratio at the Start of Third-line Chemotherapy is a Useful Prognostic Factor for Unresectable Recurrent Colorectal Cancer

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ABSTRACT

Aim : This study aimed to identify a long-term prognostic factor after second-line chemotherapy for unresectable recurrent colorectal cancer.

Methods : From 2013 through 2018, 16 patients (12 men and 4 women) who had unresectable recurrence of primary colorectal cancer after surgical resection and were given TAS-102 as a third-line chemotherapy in our institution were retrospectively enrolled in this study. The mean age of patients was 65.4 (range, 46-79) years. Patients had been given oxaliplatin with oral S-1 (tegafur, gimeracil, and oteracil potassium) for first-line chemotherapy and irinotecan with oral S-1 for second-line chemotherapy.

Results : The median survival time after second-line chemotherapy was 19.2 months. Independent contributing factors, based on Cox proportional hazards regression, to predict survival after second-line chemotherapy were the primary tumor site ($p = 0.015$) and the neutrophil-to-lymphocyte ratio (NLR) at the start of third-line chemotherapy ($p = 0.010$). Patients who survived for more than or less than 1 year did not have significant differences in mean age, sex, body mass index, primary site of disease, pathology of primary tumor, depth of primary tumor invasion, serum carcinoembryonic antigen level, serum carbohydrate antigen 19-9 level, or the tumor recurrence site. However, of the 10 factors evaluated, the only one that exhibited a significant difference between these groups of patients was the NLR at the start of third-line chemotherapy.

Conclusions : For patients who have unresectable recurrent colorectal cancer after second-line chemotherapy, the NLR at the start of third-line chemotherapy is a useful prognostic factor.

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Key words : colorectal cancer, neutrophil-to-lymphocyte ratio, prognostic factor, chemotherapy, TAS-102

INTRODUCTION

The novel oral antitumor agent TAS-102 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is recommended by the Japanese Society for Cancer of the Colon and Rectum Guidelines as a third- or fourth-line chemotherapy for patients with unresectable colorectal cancer[1]. We have reported the usefulness of TAS-102 as a third-line chemotherapy for patients with such cancers[2]. However, we have noticed highly variable prognoses in patients given TAS-102 after second-line chemotherapy. The present study aimed to identify a long-term prognostic factor after second-line

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chemotherapy for unresectable recurrent colorectal cancer.

METHODS

The Ethics Committee for Biomedical Research of the Jikei Institutional Review Board approved the protocol [29-041 (8657)], and all patients or their family members provided written informed consent. From 2013 through 2018, 16 patients (12 men, 4 women) in the Jikei University Kashiwa Hospital who had unresectable recurrence after resection of primary colorectal cancer and were given TAS-102 as third-line chemotherapy were retrospectively enrolled in this study. These 16 patients were given the regimen of oxaliplatin with oral S-1 (tegafur, gimeracil, and oteracil potassium) (SOX) as first-line chemotherapy and were then given the regimen of irinotecan with oral S-1 (IRIS) as second-line chemotherapy. Patients were included in this study only if they had demonstrated adequate organ function as shown by leukocytes $\geq$ 4,000 and $<$ 12,000/mm^3 ; thrombocytes $\geq$ 100,000/mm^3, total serum bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase $<$ 100 IU/l, and creatinine $\leq$ 1.5 mg/dl. Patients were excluded if they had a history of drug hypersensitivity or severe surgical or nonsurgical complications. The cut-off values for serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) concentrations were 50 ng/ml, which are 10 times the respective reference values[3] of 5 ng/ml and 37 U/ml. The cut-off value for the neutrophil-to-lymphocyte ratio (NLR) was 3.0[4].

Treatment schedule

Physical examinations, routine blood analyses, and measurements of CEA and CA19-9 were performed every month before chemotherapy. Computed tomography was performed every 2 months or when a patient's serum CEA value on the treatment day was higher than it had been before the initial chemotherapy. The responses of the measurable and accessible disease sites were evaluated according to the Response Evaluation Criteria in Solid Tumors[5].

As the first-line treatment the SOX regimen[6] was administered for a 3-week cycle. Oxaliplatin was infused at a dose of 130 mg/m^2 on the first day. Oral S-1 (Taiho Pharmaceutical) was then administered twice daily after meals for the next 14 days at a dosage of 80 mg/day for patients with a body surface area (BSA) $<$ 1.5 m^2 and of 100 mg/day for patients with a BSA $>$ 1.5 m^2. Oral S-1 was then withdrawn for a 6-day rest period.

As the second-line treatment the IRIS regimen[7] was administered for a 3-week cycle. Irinotecan was infused at a dose of 120 mg/m^2 on the first day. Oral S-1 was then administered twice daily after meals for the next 14 days at a dosage of 80 mg/day for patients with a BSA $<$ 1.5 m^2 and of 100 mg/day for patients with a BSA $>$ 1.5 m^2. Oral S-1 was then withdrawn for a 6-day rest period.

As the third-line treatment, TAS-102 was administered at a dose of 35 mg/m^2 after morning and evening meals 5 days a week for 2 weeks and was then withdrawn for a 14-day rest period. The regimen was repeated every 4 weeks.

Adverse events were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03[8].

Statistical analysis

Continuous variables are expressed as the mean and range. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-square test was used to compare categorical data. Postoperative survival time was examined with the Kaplan-Meier method and log-rank analysis. To determine which factors affected survival after second-line chemotherapy, Cox proportional hazard regression was used to analyzed these 7 variables : age, sex, serum CEA and CA19-9 levels at the start of third-line chemotherapy, the primary site of disease, the depth of primary tumor invasion, and the NLR at the start of third-line chemotherapy.

A *P*-value of less than 0.05 indicated significance. All data were analyzed with the software program IBM SPSS Statistics, version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

Patient characteristics

The 16 patients had a mean age of 65.4 years and a mean body mass index of 22.7 kg/m^2 (Table 1). The primary tumor was colon cancer in 7 patients and rectal cancer in 9 patients. The primary tumor was well-differentiated adenocarcinoma in 1 patient and moderately differentiated adenocarcinoma in 13 patients. The tumors were classified as T3 in 6 patients and as T4 in 10 patients. The NLR was greater

Table 1. Characteristics of the patients

Variable	$n = 16$
Mean age (range), years	65.4 (46-79)
Sex, *n* (%)	
Male	12 (75)
Female	4 (25)
Body mass index (range), kg/m^2	22.7 (21.1-25.2)
Primary tumor site, *n* (%)	
Colon	7 (44)
Rectum	9 (56)
Pathology of primary tumor, *n* (%)	
Well-differentiated adenocarcinoma	1 (6)
Moderately differentiated adenocarcinoma	13 (82)
Other	2 (12)
Depth of primary tumor invasion, *n* (%)	
T3	6 (38)
T4	10 (62)
Neutrophil-to-lymphocyte ratio, *n* (%)	
≤3	10 (62)
>3	6 (38)
Carcinoembryonic antigen, *n* (%)	
≤50 ng/ml	7 (44)
>50 ng/ml	9 (56)
Carbohydrate antigen 19-9, *n* (%)	
≤37 U/ml	11 (69)
>37 U/ml	5 (31)
Recurrent site	
Liver, *n* (%)	9 (56)
Peritoneum, *n* (%)	7 (44)
Lung, *n* (%)	4 (25)

than 3.0. in 6 patients (38%). The CEA level was greater than 50 ng/ml in 7 patients (44%). The CA19-9 level was greater than 37 U/ml in 11 patients (69%). Tumors had metastasized to the liver in 9 patients (56%) and to the lung in 7 patients (44%) and had disseminated to the peritoneum in 4 patients (25%). The median survival time after second-line chemotherapy was 19.2 months (Fig. 1).

Multivariate analyses for survival after second-line chemotherapy

Of the variables analyzed to determine whether they were independent contributing factors predicting survival after second-line chemotherapy, only 2 were identified : primary tumor location ($p = 0.015$) and the NLR at the start of third-line chemotherapy ($p = 0.010$) (Table 2).

Comparison of survival time after second-line chemotherapy between high and low NLR

The survival time after second-line chemotherapy was significantly shorter for patients with an NLR > 3.0 than for patients with an NLR ≤ 3.0 ($p < 0.001$) (Fig. 2).

Comparison of patients who survived for more or less than 1 year after second-line chemotherapy

A comparison of patients who survived for more or less than 1 year after second-line chemotherapy found not significant differences in mean age, sex, body mass index, primary site of disease, pathology of primary tumor, the

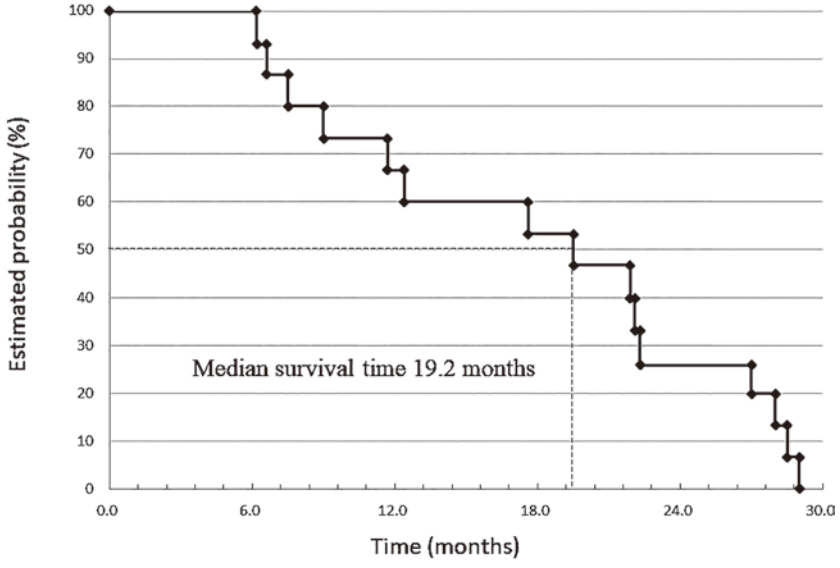

Fig. 1. Overall survival time after second-line chemotherapy

Table 2. Multivariate analyses using the Cox proportional hazard model for survival after second-line chemotherapy

Variable	Hazard ratio (95% confidence interval)	*P* value
Age, years		
≥70	1.976 (0.339-11.514)	0.449
<70	1	
Sex		
Female	0.177 (0.022-1.435)	0.105
Male	1	
Carcinoembryonic antigen		
>50 ng/ml	11.098 (0.759-162.327)	0.079
≤50 ng/ml	1	
Carbohydrate antigen 19-9		
≤37 U/ml	1	
>37 U/ml	0.226 (0.002-24.010)	0.533
Primary tumor site		
Rectum	51.971 (2.128-1269.391)	0.015
Colon	1	
Depth of primary tumor invasion		
T3	1	
T4	1.951 (0.354-10.753)	0.443
NLR		
≤3	1	
>3	130.391 (3.220-5279.907)	0.010

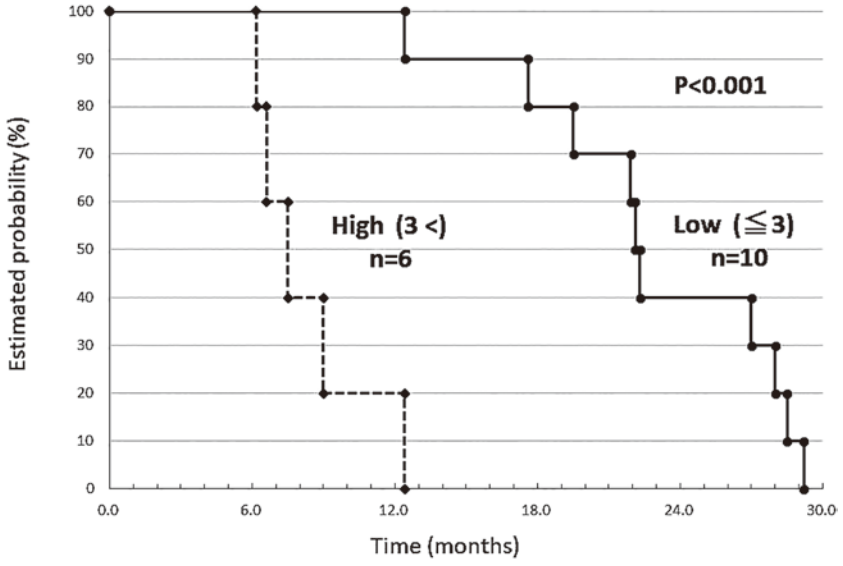

Fig. 2. Comparison of survival after second-line chemotherapy between patients with the NLR ≤ 3 or >3

depth of primary tumor invasion, serum CEA level, CA19-9 level, and the recurrence site of disease. However, of the 10 factors evaluated, the only factor that exhibited a significant difference was the NLR at the start of third-line chemotherapy (Table 3).

Adverse effects after second-line chemotherapy using TAS-102

For chemotherapy regimens using TAS-102 no adverse effects were more severe than grade 2. When the white blood cell count was less than 3,000/μL, the rest period was extended by 14 days.

Table 3. Comparison of patients who survived more or less than 1 year after second-line chemotherapy

Factor	Survival < 1 year (n = 6)	Survival > 1 year (n = 10)	p-Value
Mean age (range), years	66.0 (59-78)	65.0 (46-79)	0.947
Sex, n (%)			0.233
Male	6 (100)	6 (60)	
Female	0 (0)	4 (40)	
Body mass index (range), kg/m^2	22.2 (21.1-25.0)	23.0 (21.0-26.2)	0.345
Primary tumor site, n (%)			0.242
Colon	1 (17)	6 (60)	
Rectum	5 (83)	4 (40)	
Pathology of primary tumor, n (%)			0.691
Well-differentiated adenocarcinoma	0 (0)	1 (10)	
Moderately differentiated adenocarcinoma	5 (83)	8 (80)	
Other	1 (17)	1 (10)	
Depth of primary tumor invasion, n (%)			1.000
T3	2 (33)	4 (40)	
T4	4 (67)	6 (60)	
Neutrophil-to-lymphocyte ratio, n (%)			0.008
≤3	1 (17)	9 (90)	
>3	5 (83)	1 (10)	
Carcinoembryonic antigen, n (%)			0.633
≤50 ng/ml	4 (67)	5 (50)	
>50 ng/ml	2 (33)	5 (50)	
Carbohydrate antigen 19-9, n (%)			0.588
≤37 U/ml	1 (17)	4 (40)	
>37 U/ml	5 (83)	6 (60)	
Recurrent site			0.497
Liver, n (%)	3 (50)	6 (60)	
Lung, n (%)	4 (67)	3 (30)	
Peritoneum, n (%)	1 (17)	3 (30)	

Discussion

To perform first-line or second-line chemotherapy for patients who have colorectal cancer that is unresectable and recurrent, regimens widely used include the infused agents fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) and the orally administered agents S-1 combined with oxaliplatin (SOX)[6] or irinotecan (IRIS)[7] and capecitabine combined with oxaliplatin (CapeOX)[9] or irinotecan (XELIRI)[10]. However, unlike first- and second-line chemotherapy, third-line chemotherapy has no effective regimens. We have reported that the usefulness of TAS-102 as third-line chemotherapy for patient with unresectable recurrent colorectal cancer[2]. At that time, we have noticed highly variable prognoses in patients given TAS-102 after second-line chemotherapy.

In the present study, the NLR at the start of TAS-102 administration as third-line chemotherapy was identified as an independent contributing factor to predict survival after second-line chemotherapy. The NLR, which is defined by the absolute number of neutrophils divided by the absolute number of lymphocytes, is considered an inflammatory biomarker. Several studies have found that an elevated NLR is associated with a poor prognosis in patients with various malignant diseases[11-15]. Apparently, the effectiveness of chemotherapy is greatly involved with not only the chemosensitivity to anticancer drugs but also with immunosuppression.

Although the NLR cut-off values used in previous studies have ranged from 3 to 5, the optimal ratio has not been established[16]. However, a previous study has found that the optimal cut-off value to predict survival after TAS-102 treatment of patients with metastatic colorectal cancer was 5.0[17]. Unfortunately, 48.5% of all patients in that study

had received TAS-102 as a fourth-line or later treatment. Furthermore, the cut-off value was not calculated with receiver operating characteristic curve analysis.

Because the optimal NLR cut-off value had not been established, for the present study the NLR value we chose, on the basis of receiver operating characteristic curve analysis[4], was 3.0. When patients have an NLR greater than 3.0 at the start of third-line chemotherapy, an optimal regimen for this degree of immunosuppression should be carefully selected for third-line or fourth-line chemotherapy or both.

In conclusion, the NLR at the start of third-line chemotherapy is a useful prognostic factor for patients with unresectable colorectal cancer after second-line chemotherapy ; however, a large-scale prospective study is needed.

Authors have no conflict of interest.

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