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Neutrophil-lymphocyte Ratio at the Beginning of Third-line Chemotherapy Seems to be a Useful Predictor for Unresectable Colorectal Cancer

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Abstract

Aim: This study aimed to evaluate a long-term outcome predictor after second-line chemotherapy for unresectable colorectal cancer.

Methods: Between 2013 and 2018, sixteen patients (twelve males, four females) with unresectable colorectal cancer who were administered TAS-102 as third-line chemotherapy in our institution were retrospectively enrolled in this study. The mean age was 65.4 (range: 46-79) years. Patients were administered oxaliplatin with oral S-1 (tegafur, gimeracil, oteracil potassium) (SOX) as first-line chemotherapy followed by irinotecan with oral S-1 (IRIS) as second-line chemotherapy.

Results: The median survival time after second-line chemotherapy was 19.2 months. Significant differences in mean age, gender, body mass index, primary site of disease, pathology of primary tumor, depth of primary tumor invasion, serum carcinoembryonic antigen (CEA) level, serum carbohydrate antigen 19-9 (CA19-9) level, and recurrence site of disease were not observed between patients with less than one year of survival versus greater than one year of survival. However, neutrophil-lymphocyte ratio (NLR) at the beginning of third-line chemotherapy was the only factor of the ten evaluated that exhibited a significant difference. Primary tumor site (p=0.015) and NLR at the beginning of third-line chemotherapy (p=0.010) were independent contributing factors to predict survival after second-line chemotherapy based on Cox proportional hazards regression.

Conclusion: NLR at the beginning of third-line chemotherapy is a useful predictor for unresectable colorectal cancer after second-line chemotherapy.

Introduction

TAS-102 (Taiho Pharmaceutical Co. Ltd, Tokyo, Japan) is a novel oral antitumor agent recommended as third- or fourth-line chemotherapy for patients with unresectable colorectal cancer by the Japanese Society for Cancer of the Colon and Rectum Guidelines [1]. We have reported the usefulness of TAS-102 as third-line chemotherapy for patient with unresectable colorectal cancer [2]. However, we have noticed highly variable prognoses in patients administered TAS-102 after second-line chemotherapy. This study aimed to evaluate a long-term outcome predictor after second-line chemotherapy for unresectable 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. Between 2013 and 2018, sixteen patients (twelve males, four females) with unresectable colorectal cancer who were administered TAS-102 as third-line chemotherapy in our institution were retrospectively enrolled in this study. The mean age was 65.4 (range: 46-79) years (Table 1). These 16 patients were given oxaliplatin with oral S-1 (tegafur, gimeracil, oteracil potassium) (SOX) as first-line chemotherapy,

followed by the administration of irinotecan with oral S-1 (IRIS) as second-line chemotherapy. Patients were only included in this study if they demonstrated adequate organ function (4,000≤leukocytes<12,000/mm3; thrombocytes, ≥100,000/ mm3; total serum bilirubin, ≤1.5 mg/dl; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), <100 IU/l; and creatinine, ≤1.5 mg/dl). Patients with a history of drug hypersensitivity or serious surgical and non-surgical complications were excluded. The cutoff values for serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) concentrations were 50 ng/ml, which is tenfold of the normal limit [3] of 5 ng/ml, and 37 U/ml, respectively. The cutoff value for the neutrophil-lymphocyte ratio (NLR) was 3.0 [4].

Treatment schedule.

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

SOX [6] was employed as the first-line treatment. Oxaliplatin at 130 mg/m^2 was administered on the first day followed by 14-day administration and 6-day withdrawal of oral S-1 (Taiho Pharmaceutical, Tokyo, Japan) at 80 mg or 100 mg per day according to the patient's body surface area (BSA). Specifically, 80 mg/day S-1 was administered to those patients with BSA<1.5 m^2, and 100 mg/day S-1 was administered to those patients with BSA>1.5 m^2. S-1 was administered orally twice daily after meals.

Irinotecan with oral S-1 (IRIS) [7] was employed as the second-line treatment. Irinotecan at 120 mg/m^2 was administered on the first day followed by 14-day administration and 6-day withdrawal of oral S-1 (Taiho Pharmaceutical, Tokyo, Japan) at 80 mg or 100 mg per day according to the patient's BSA. Specifically, 80 mg/day S-1 was administered to those patients with BSA<1.5 m^2, and 100 mg/day S-1 was administered to those patients with BSA>1.5 m^2. S-1 was administered orally twice daily after meals.

In the third-line treatment, TAS-102 at 35 mg/m^2 was administered twice daily after morning and evening meals 5 days a week for 2 weeks followed by a 14-day rest period, thus completing one treatment cycle. 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 for the comparison of continuous variables, and the chi-square test was used for the comparison of categorical

data. Postoperative survival time was examined by the Kaplan-Meier method and log-rank analysis. Variables affecting postoperative survival were analyzed using the Cox proportional hazards regression. A P-value of less than 0.05 indicated significance. All data were analyzed with IBM SPSS Statistics, version 24.0 (IBM Japan, Ltd, Tokyo, Japan).

Results

Comparison between groups with less than versus greater than one year survival after second-line chemotherapy

The median survival time after second-line chemotherapy was 19.2 months (Figure 1). In comparison no significant differences in mean age, gender, body mass index, primary site of disease, pathology of primary tumor, depth of primary tumor invasion, serum CEA level, CA19-9 level, and recurrence site of disease were not observed between patients with less than one year of survival compared with those with greater than one year survival. However, NLR at the beginning of third-line chemotherapy was the only factor of the ten evaluated factors that exhibited a significant difference (Table 2).

Multivariate analyses for postoperative recurrence

To determine variables affecting survival after second-line chemotherapy, seven variables (age, gender, serum CEA and CA19-9 levels at the beginning of third-line chemotherapy, primary site of disease, depth of primary tumor invasion, and NLR at the beginning of third-line chemotherapy) were analyzed using Cox proportional hazard regression. Only two factors, primary tumor location (p=0.015) and NLR at the beginning of third-line chemotherapy (p=0.010), were identified as independent contributing factors to predict survival after second-line chemotherapy. (Table 3).

Adverse effects after second-line chemotherapy using TAS-102

No serious adverse effects greater than grade 2 were noted for chemotherapy regimens using TAS-102. When white blood cell counts were less than 3,000, a 14-day rest period was added to the regular rest period.

Discussion

The infusion of fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) as well as oral drugs combined with either oxaliplatin (SOX [6], CapeOX [9]) or irinotecan (IRIS [7], XELIRI [10]) have been widely used as first-line or second-line chemotherapy for unresectable colorectal cancer. However, there are no effective regimens for third-line chemotherapy compared with

first- or second-line chemotherapy. We have reported that the usefulness of TAS-102 as third-line chemotherapy for patient with unresectable colorectal cancer [2]. However, we have noticed highly variable prognoses in patients administered TAS-102 after second-line chemotherapy.

In this study, NLR at the beginning of 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 reported that an elevated NLR is associated with a poor prognosis in patients with various malignant diseases [11–15]. The effectiveness of chemotherapy seems greatly involved in not only chemosensitivity of anticancer drugs but also immunosuppression. The optimal cutoff value was 3.0 based on receiver operating characteristic (ROC) curve analysis [4]. When patients exhibit an NLR greater than 3.0 at the beginning of third-line chemotherapy, we should carefully select an optimal regimen as third- and/or fourth-line chemotherapy.

In conclusion, NLR at the beginning of third-line chemotherapy seems to be a useful predictor for unresectable colorectal cancer after second-line chemotherapy; however, a large-scale prospective study is needed.

Abbreviations

NLR: Neutrophil-lymphocyte ratio; SOX: S-1 plus oxaliplatin; IRIS: S-1 plus irinotecan; CapeOX: Capecitabine plus oxaliplatin; FOLFOX: Infusion of fluorouracil and leucovorin combined with oxaliplatin; FOLFIRI: Infusion of fluorouracil and leucovorin combined with irinotecan; XELIRI: Capecitabine plus irinotecan; CEA: Serum carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CT: Computed tomography; RECIST: Response Evaluation Criteria in Solid Tumors; ROC: Receiver operating characteristic.

Declarations

Ethics approval and consent to participate

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.

Consent for publication

There is no use of details, images, or videos relating to an individual person.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no competing interests.

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Authors' contributions

HK and NO performed operation. All authors analyzed and interpreted the patient data, and have been involved in drafting the manuscript. TA had given final approval of the version to be published. All authors read and approved the final manuscript.

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References

1. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2019;25(1):1–42.
2. Kawahara H, Mouri T, Ishida K, Matsumoto N, Akiba T, Yanaga K. Usefulness of TAS-102 as Third-line Chemotherapy for Metastatic Colorectal Cancer. Anticancer Res. 2018;38(4):2419–22.
3. Hashizume R, Kawahara H, Ogawa M, Suwa K, Eto K, Yanaga K. CA19-9 Concentration After First-line Chemotherapy Is Prognostic Predictor of Metastatic Colon Cancer. In Vivo. 2019;33(6):2087–93.
4. Hiramoto Y, Kawahara H, Matsumoto T, Takeda M, Misawa T, Yanaga K. Preoperative Neutrophil-lymphocyte Ratio Is a Predictor of High-output Ileostomy After Colorectal Surgery. Anticancer Res. 2019;39(6):3265–8.

5. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
6. Yamada Y, Tahara M, Miya T, et al. Phase I/II study of oxaliplatin with oral S-1 as first-line therapy for patients with metastatic colorectal cancer. Br J Cancer. 2008;98(6):1034–8.
7. Choi YH, Kim TW, Kim KP, et al. A Phase II study of clinical outcomes of 3-week cycles of irinotecan and S-1 in patients with previously untreated metastatic colorectal cancer: influence of the UGT1A1 and CYP2A6 polymorphisms on clinical activity. Oncology. 2012;82(5):290–7.
8. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. 2010 http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5 × 7.pdf.
9. Twelves CJ, Butts CA, Cassidy J, et al. Capecitabine/oxaliplatin, a safe and active first-line regimen for older patients with metastatic colorectal cancer: post hoc analysis of a large phase II study. Clin Colorectal Cancer. 2005;5(2):101–7.
10. Patt YZ, Lee FC, Liebmann JE, et al. Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol. 2007;30(4):350–7.
11. Shimada H, Takiguchi N, Kainuma O, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer. 2010;13:170–6.
12. Chua W, Charles KA, Baracos VE, et al. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104:1288–95.
13. Motomura T, Shirabe K, Mano Y, et al. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol. 2013;58:58–64.
14. Yoshizumi T, Ikegami T, Yoshiya S, et al. Impact of tumor size, number of tumors and neutrophil-to-lymphocyte ratio in liver transplantation for recurrent hepatocellular carcinoma. Hepatol Res. 2013;43:709–16.
15. Eto S, Kawahara H, Matsumoto T, Hirabayashi T, Omura N, Yanaga K. Preoperative Neutrophil-Lymphocyte Ratio Is a Predictor of Bowel Obstruction Due to Colorectal Cancer Growth. Anticancer Res. 2019;39(6):3185–9.

Tables

Due to technical limitations, table 1, table 2 and table 3 are only available as a download in the Supplemental Files section.

Figures

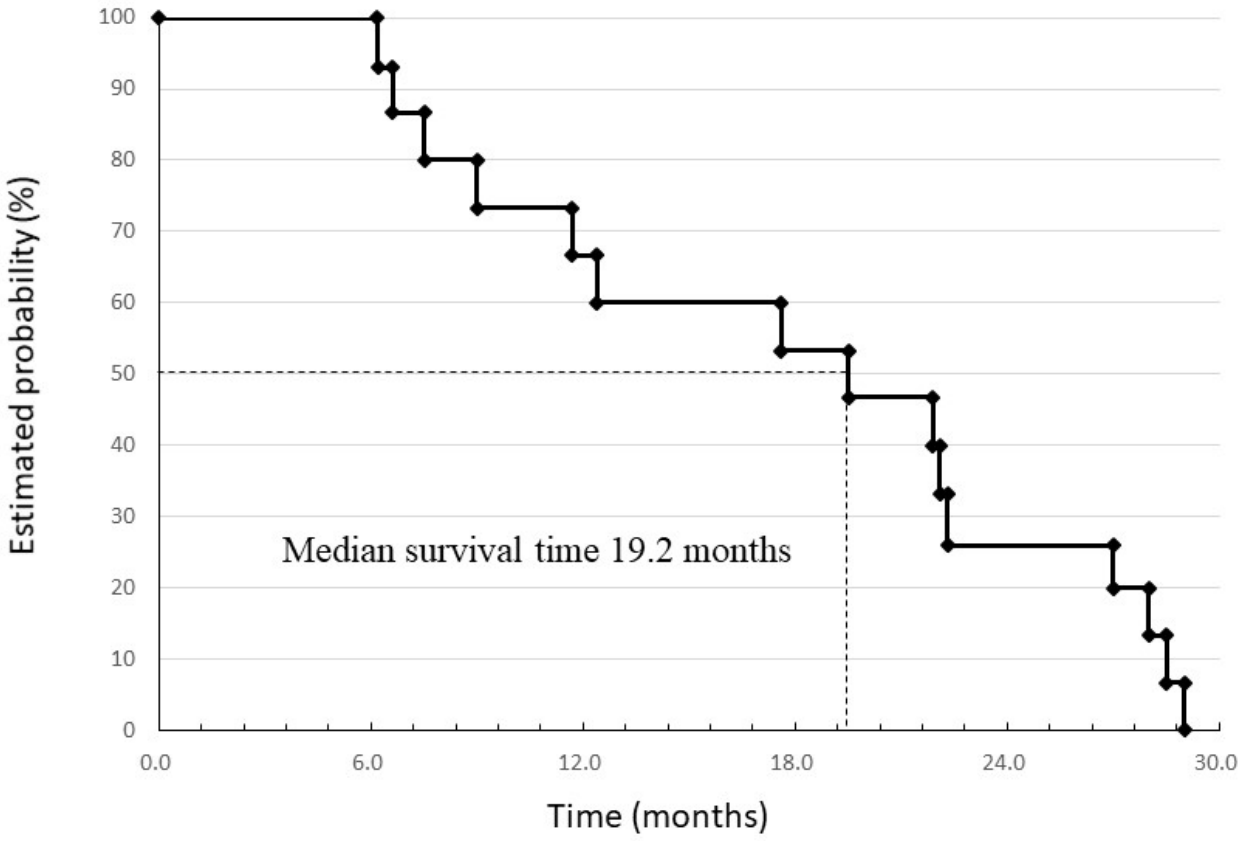

Figure 1

Overall survival time after second-line chemotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table3TAS102.xlsx
- Table1TAS102.xlsx
- Table2TAS102.xlsx