Original Article

A single-center retrospective analysis of the efficacy and safety of a modified regimen of irinotecan plus S-1 (IRIS) with molecular targeting agents as second-line chemotherapy in Japanese patients with recurrent or nonresectable colorectal cancer

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Background: As the second-line chemotherapy for stage IV recurrent or nonresectable colorectal cancer, our hospital started a modified treatment regimen comprising of irinotecan plus S-1 (IRIS) [tegafur/gimeracil/oteracil (S-1)] plus molecular targeting agents (MTAs), i.e., an epidermal growth factor receptor (EGFR) inhibitor such as panitumumab (P-mab) or cetuximab (C-mab) or vascular endothelial growth factor (VEGF) inhibitor such as bevacizumab (B-mab) since October 2012. The purpose of this study is to evaluate the efficacy and safety of this modified regimen.

Methods: This retrospective study included 41 patients with advanced recurrent colorectal cancer at our hospital whom at least 3 courses of chemotherapy were conducted from January 2015 to December 2021. Based on the location of the primary tumor, patients were classified into two group (right-sided group, proximal to the splenic curve, and left-sided, distal to the splenic curve). We assessed archived data on RAS and BRAF status and UGT1A1 polymorphisms and use of the VEGF inhibitor bevacizumab (B-mab) and the EGFR inhibitors panitumumab (P-mab) and cetuximab (C-mab). In addition, progression-free survival rate (36M-PFS) and the overall survival rate (36M-OS) were calculated. Furthermore, the respective median survival time (MST), the median number of treatment courses; the objective response rate (ORR) and clinical benefit rate (CBR) and the incidence of adverse events (AEs) were assessed as well.

Results: There were 11 patients (26.8%) in the right-sided group, and 30 patients (73.2%) in the left-sided group. There were 19 patients with RAS wild type (46.3%) (1 in the right sided group and 18 in the left sided group). P-mab was used for 16 of these patients (84.2%), C-mab for 2 (10.5%), and B-mab for 1 (5.3%); the remaining 22 patients (53.7%). Ten patients in the right group and 12 patients in the left group were a mutated type and received B-mab. BRAF testing was performed in 17 patients (41.5%); as more than 50% of patients (58.5%) were included before the assay's introduction. Five patients in the right-sided group and 12 patients in the left-sided group had wild type. There was no mutated type. UGT1A1 polymorphism was tested in 16/41 patients: Eight were wild type (8/41 patients, 19.5%) and 8, mutated type. Regarding the *6/*28 double heterozygous type, there was only 1 patient in the right-sided group and the remaining 7 patients were in the left-sided group. The total number of chemotherapy courses was 299, and the median number, 6.0 (range, 3–20). PFS, OS, and MST were as follows: 36M-PFS (total/Rt/Lt), 6.2%/0.0%/8.5% (MST; 7.6/6.3/8.9 months); and 36M-OS (total/Rt/Lt), 32.1%/0.0%/44.0% (MST; 22.1/18.8/28.6 months).

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The ORR and CBR were 24.4% and 75.6%, respectively. The majority of AEs were grades 1 or 2 and were improved with conservative treatment. Grade 3 leukopenia was observed in 2 cases (4.9%), neutropenia in 4 cases (9.8%), and malaise/nausea/diarrhea/perforation in 1 case each (2.4%). Grade 3 leukopenia (2 patients) and neutropenia (3 patients) were more commonly observed in the left-sided group. Diarrhea and perforation were also common in the left-sided group.

Conclusions: This second-line modified IRIS regimen with MTAs is safe and effective and results in good PFS and OS.

Keywords: Colorectal cancer; chemotherapy; molecular targeting therapy; irinotecan plus S-1 (IRIS); recurrent/non-resectable cancer

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Introduction

Advanced or recurrent colorectal cancer is common in clinical practice. In recent years, vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab (B-mab), ramucirumab, and VEGF-targeted fusion proteins have been recommended for right-sided advanced or recurrent colorectal cancer derived from the midgut. However, such cancers have a high expression rate of BRAF and a larger tumor mass and worse prognosis than left-sided colorectal cancers, so VEGF inhibitors may not achieve optimal results (1,2). Therefore, for BRAF-positive colorectal cancer, triplet chemotherapy with cetuximab (C-mab), encorafenib, and binimetinib and doublet chemotherapy with C-mab and encorafenib are also recommended. Nevertheless, these treatment regimens are rarely used, and only a few clinical studies have evaluated them (3-5).

Epidermal growth factor receptor (EGFR) inhibitors [e.g., panitumumab (P-mab) or C-mab] are broadly used for RAS/BRAF wild-type advanced recurrent or nonresectable colorectal cancer. These drugs are also used for left-sided advanced or recurrent colorectal cancer derived from the hindgut (including the rectum), and studies have reported higher survival rates with EGFR inhibitors than with VEGF inhibitors (6-9).

Right-sided colorectal cancers have microsatellite instability (MSI), which is considered as a consensus molecular subtype (CMS) 1. In contrast, chromosomal instability (CIN) is often observed in left-sided colorectal cancers. Studies on primary colorectal cancer have found differences in treatment response and outcome depending on the location of the tumor (10,11). In Japan, an immune checkpoint inhibitor (ICI) (e.g., pembrolizumab) is the first-line therapy for MSI-positive advanced recurrent or nonresectable colorectal cancer (a rare type of cancer) (12,13).

Chemotherapy for stage IV colorectal cancer has made significant advancements since the use of FOLFIRI (folinic acid, fluorouracil, and irinotecan) and FOLFOX (5-fluorouracil/leucovorin combined with oxaliplatin). However, better results were achieved when cyramza or zaltrapis combined with FOLFIRI was used as the second-line therapy.

In clinical practice, B-mab-based combination chemotherapy is often used as first-line chemotherapy for advanced recurrent or nonresectable metastatic colorectal cancer; this treatment was studied in many Phase III clinical

Highlight box

Key findings

- Second-line treatment with the modified IRIS regimen (irinotecan 85 mg/m^2) is associated with good PFS and OS and causes few serious adverse events.

What is known and what is new?

- The dose reduction rate of irinotecan was only 9.8% and the majority of AEs were grades 1 or 2. There were only 10 grade 3 adverse events regardless of all UGT1A1 polymorphism subtypes.
- Although we used a lower dose treatment regimen, we were still able to achieve a good PFS, OS, ORR and CBR.

What is the implication, and what should change now?

- Second-line treatment with the modified IRIS regimen comprising minimal chemotherapy doses for stage IV recurrent or nonresectable colorectal cancer has demonstrated good efficacy and safety.

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studies and has the advantage that gene testing is not required (1,5,14). Moreover, in recent years, nonresectable stage IV colorectal cancer has also been treated by chemotherapy combined with conversion surgery (CS-R0) (15). However, the clinical presentation of stage IV colorectal cancer with remote metastases varies and ranges from cases with just 1 to 2 metastatic foci in the liver or lung to those with 5-cm or larger metastatic foci scattered throughout both lobes of the liver and the lung. In addition, only a few studies have evaluated standardized treatment regimens for metastatic colorectal cancer (16,17).

In Japanese and Asian adults, the average height and body weight are about 165 to 175 cm and 65 to 70 kg, respectively, which is lower than the values in Western adults (about 175–180 cm and >85–90 kg, respectively), and the standard body surface area is 1.48 m^2 (*vs.* 1.73 m^2 in Western adults). Accordingly, the treatment regimens FOLFOX4 and FOLFOX6 have frequently been studied in Japanese people because of their smaller body frame (18,19). As we have previously reported, when determining the dose, we aimed to use a minimal chemotherapy dose (20,21). Therefore, at our hospital, we frequently use B-mab-CAPOX (Cape + L-OHP) as the first-line therapy for stage IV recurrent or nonresectable colorectal cancer, and we have reported on the efficacy and safety of this approach (20,22,23). For this type of cancer, in January 2015 we introduced a standardized second-line therapy with a modified IRIS regimen, i.e., irinotecan plus S-1 (IRIS) [tegafur/gimeracil/oteracil (S-1)] regimen plus molecular targeting agents (MTA), i.e., the EGFR and VEGF inhibitors B-mab, C-mab, and P-mab. The objective of this retrospective analysis was to evaluate the efficacy and safety of this new second-line chemotherapy stratified by right-sided *vs.* left-sided tumor location. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-899/rc).

Methods

Patients and first-line therapy

At our hospital, surgical resection is the first-line therapy for stage IV colorectal cancer with liver or lung metastases if the tumor is macroscopically resectable with a negative margin (R0). After surgery, intensive therapy is provided with chemotherapy and radiation therapy. In cases where R0 resection is not possible, chemotherapy is used as the first-line therapy to achieve CS-R0, and diagnostic imaging with ultrasound or a computed tomography (CT) scan is performed every 3 to 4 months to evaluate the effectiveness of treatment. However, in Stage IV colorectal cancer, primary resection is performed when there is bleeding or bowel obstruction or when the patient requests resection.

In October 2012, we started using combination therapy with MTAs, i.e., the EGFR and VEGF inhibitors B-mab, C-mab, and P-mab, as second-line systemic chemotherapy for stage IV recurrent or nonresectable colorectal cancer. Then, in January 2015, we introduced MTA plus IRIS as the standardized second-line therapy. We designed this modified IRIS MTA regimen for the following reasons: (I) there is no need to implant a reservoir or use extended sustained direct intravenous infusion; (II) the outpatient visit is short, and patients only need to visit the outpatient clinic twice per course (on day 1 and day 15); and (III) the S-1 treatment is taken orally for 2 weeks at home.

From January 2015 to December 2021, a total of 299 courses of this standardized second-line chemotherapy were performed in 41 patients at our hospital (24-26). At the time of admission to the hospital, these patients had a diagnosis of primary colorectal cancer, as confirmed by biopsy (via colonoscopy) and histopathology; recurrent colorectal cancer with metastases to the liver, lungs, and distant lymph nodes diagnosed by ultrasonography, CT scan, magnetic resonance imaging, and positron emission tomography; and Stage IV advanced colorectal cancer. The Union for International Cancer Control TNM classification stages of colorectal cancer (eighth edition) was used for staging assessment (27). First-line systemic chemotherapy was based on oxaliplatin in 95.1% (39/41) of these patients; among these patients, 89.7% (35/39 patients) received combination treatment with B-mab and CAPOX (oxaliplatin and capecitabine).

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by Chemotherapy Committee at Tokai University Hachioji Hospital and the institutional review board for clinical research at Tokai University Medical School (No. 22 R-023), and informed consent was taken from all the patients.

Second-line therapy

We previously used FOLFOX4/6 as a 4-week course with 2 weeks on/2 weeks off of L-OHP (85 mg/m^2). Based on our past experiences, we established a modified treatment

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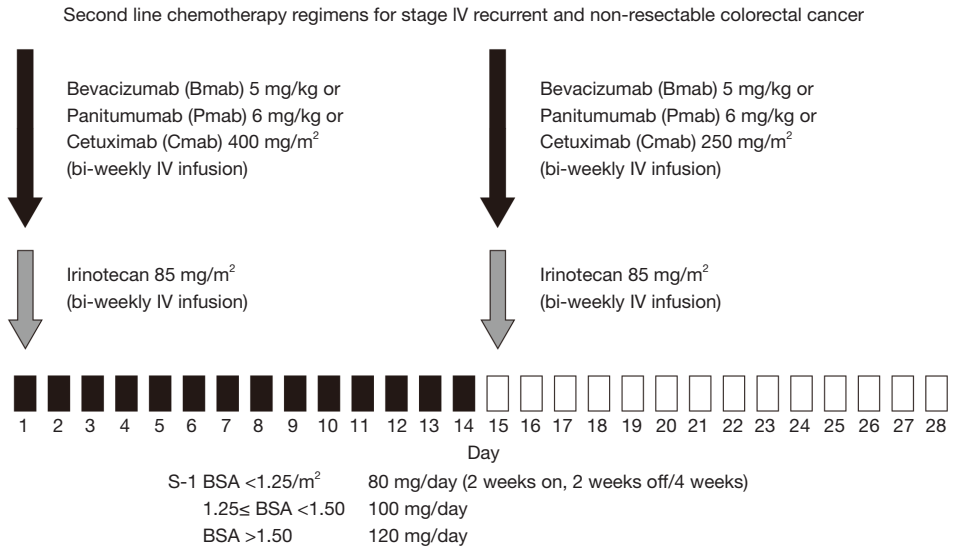

Figure 1 Modified IRIS regimen [irinotecan plus tegafur/gimeracil/oteracil (S-1)] with molecular targeting agents. Similar to FOLFOX 6, irinotecan (85 mg/m^2) was administered via direct intravenous infusion at the outpatient clinic on day 1 and day 15 (4 weeks per course), and S-1 was administered orally according to the package insert (80–120 mg/m^2; 2 weeks on/2 weeks off). IRIS, irinotecan plus S-1; BSA, body surface area; S-1, tegafur/gimeracil/oteracil.

regimen suitable for Japanese patients. Similarly, we use a lower dose of irinotecan (85 mg/m^2) than the standard dose of 100–150 mg/m^2 (i.e., a dose reduction of greater than or equal to 15% compared with the standard dose in the US/EU). Furthermore, this regimen was added with S-1 (80 to 120 mg/m^2) plus an EGFR inhibitor such as panitumumab (6 mg/kg) (P-mab) or cetuximab (day 1 400 mg/m^2, day 15 250 mg/m^2) (C-mab) or VEGF inhibitor such as bevacizumab (5 mg/kg) (B-mab). In our modified IRIS regimen, an MTA and irinotecan are administered at the outpatient clinic by direct intravenous infusion on day 1 and day 15 and S-1 is orally given as a 4-week cycle at a dose of 80 to 120 mg/m^2 for 2 weeks followed by 2 weeks off (*Figure 1*) (21,28-30). We use these regimens as the standard second-line regimen for stage IV recurrent or nonresectable colorectal cancer.

Genomic analysis and MTA treatment

In this study, we reviewed the following genomic characteristics of patients: RAS (wild or mutated), BRAF status (wild or mutated), and UGT1A1 polymorphism (*6 or *28 heterozygous type, *6/*28 double heterozygous type). Patients with wild-type RAS status were treated with P-mab or C-mab, and those with mutated status, with B-mab. During the study period (January 2015 to December 2021), UGT1A1 polymorphism type and BRAF status were not tested in all patients because these tests were no longer routinely covered by health insurance after introduction of UGT1A1 in 2008 and of BRAF in 2018; therefore, data on UGT1A1 polymorphism type and BRAF status were missing in some patients. The total and median numbers of chemotherapy courses were calculated by using the initiation day of MTA-IRIS second-line treatment as the reference.

Evaluation of efficacy and safety

The tumor location was classified into a right-sided group if a tumor was present in the cecum, ascending colon, or transverse colon up to the splenic curve, and a left-sided group if a tumor was present from the splenic curve, in the descending colon, sigmoid colon, or rectum. We calculated the progression-free survival (PFS) and overall survival (OS) rates and median survival time (MST) at 36 months (36M-PFS, 36M-OS). For PFS, the first treatment day of the first course of second-line therapy was used as the reference point, and PFS was defined as the time to progressive disease (PD) confirmed by CT scan or death from any cause. For OS, the first treatment day of the first course of second-line therapy was used as the reference point and was defined as death from any cause.

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Table 1 Background of patients with recurrent or nonresectable colorectal cancer

Characteristics	Total cases (n=41)	Right side† group (n=11)	Left side† group (n=30)	P value
Gender, n				0.413
Male	31	7	24	
Female	10	4	6	
Median age at 2nd line administration [range], y	67 [23–79]	70 [23–78]	67 [48–79]	0.965
Second line chemotherapy drug type, n				0.137
Bevacizumab (B-mab)	23	9	14	
Panitumumab (P-mab)	16	2	14	
Cetuximab (C-mab)	2	0	2	
Median number of 2nd line courses [range], n	6 [3–20]	6 [3–13]	6.5 [3–20]	0.375
Classification stage‡ at initial diagnosis, n				0.687
Stage I	2	1	1	
Stage II	4	0	4	
Stage III	11	2	9	
Stage IV	24	8	16	

†, location of the primary tumor side; ‡, UICC TNM classification stage of colorectal cancer (Eighth edition).

As an additional efficacy assessment, we evaluated objective tumor response as the objective response rate (ORR), defined as complete response (CR) or partial response (PR), and the clinical benefit rate (CBR), defined as CR, PR, or stable disease (SD) at 6 months or later. Data on dose reduction rates and dose-interval prolongation rates were also analyzed.

Adverse events (AEs) during and after three chemotherapy courses were evaluated according to the Common Terminology Criteria of Adverse Events (CTCAE) version 5.0. AEs were assessed in the total patient population and also for each UGT1A1 polymorphism type in the patients with data on UGT1A1 polymorphism.

Statistical analysis

The Kaplan-Meier method was used to calculate 36M-PFS, 36M-OS, MST, and the respective 95% confidence interval (95% CI). PFS was calculated from the first day of treatment of the second-line therapy. CT imaging was used to determine PD. OS was from the first day of treatment of the second-line therapy to the day of death. 36M-PFS, 36M-OS, MST, 95% CI were calculated by Kaplan-Meier method. Furthermore, comparison between the right-sided and left-sided groups, hazard ratio, and 95% CI were calculated by Cox proportional hazard regression model. For comparison of the patient characteristics between the two groups, age and the number of courses of the second-line therapy were tested by non-parametric Mann-Whitneys U. Gender, type of drugs used for second-line therapy, classification stage, RAS status, BRAF status, UGT1A1 polymorphism, dose reduction, dose-interval prolongation, response, Performance status, ORR, and CBR were tested by chi-square test or Fischer's exact probability test. In all tests, <0.05 was considered statistically significant. Statistical analyses were conducted with IBM SPSS Statistics for Windows Version 25.0 (RRID:SCR_016479; IBM Corp, Armonk, NY, USA).

Results

Patient characteristics, including the stages of cancer in the overall group of patients, are shown in *Table 1*. The group included more men than women. Concerning the tumor location, there were 11 patients (26.8%) in the right-sided group and 30 patients (73.2%) in the left sided. Thus, more patients had a primary tumor that was located on the left side. The most common location of the primary tumor was the rectum (17 patients, 41.5%), followed by the ascending colon (8 patients, 19.5%), and the majority of patients had

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Table 2 Comparison of genomic characteristics of patients with recurrent or nonresectable colorectal cancer

Genomic characteristics	Total cases (n=41)	Right side† group (n=11)	Left side† group (n=30)	P value
RAS status, n				<0.001
Wild-type	19	1	18	
Mutated_codon12	16	5	11	
Mutated_codon13	5	4	1	
Mutated_codon12/13	1	1	0	
BRAF status, n				>0.999
Wild-type	17	5	12	
Mutated	0	0	0	
Unknown	24	6	18	
UGT1A1 polymorphism, n				0.305
wild-type	8	3	5	
*6 heterozygous type	4	0	4	
*28 heterozygous type	3	0	3	
*6*28 double heterozygous type	1	1	0	
Unknown	25	7	18	

†, location of the primary tumor side.

stage IV cancer (24/41 patients, 58.5%) at the first diagnosis on arrivals. Among Stage IV cancer, the primary tumor was resected in 7/24 patients (29.2%).

Genomic analysis and MTA treatment

The results of genomic analysis and the RAS status-based MTA treatment are shown in *Table 2*. Mutated type RAS status was more common than wild type (22 patients, 53.7%). Among patients with wild-type RAS status, P-mab was used for almost all patients (84.2%) and only 2 patients (10.5%) received C-mab. One [1] patient received B-mab due to patient's choice. All patients with mutated type RAS status received B-mab; 18/19 wild-type patients were in the left sided group; 12/22 patients with mutated type were in the left sided group (*Table 2*).

UGT1A1 polymorphism type was tested in 16/41 (39%) of patients. In these patients, the same number had wild type as had mutated type (8/41 each, 19.5%). Among the patients with mutated type UGT1A1 polymorphism, *6 heterozygous type was the most common polymorphism (9.8%), followed by *28 heterozygous type (7.3%) and *6/*28 double heterozygous type (2.4%). Only 1 patient in *6/*28 double heterozygous type was in the right-sided group, while the remaining patients were in the left-sided group. All 8 patients with heterozygous type UGT1A1 polymorphism were started on a lower dose of irinotecan (50–80 mg/m^2) (*Table 2*).

Efficacy

The 41 patients collectively received 299 chemotherapy courses. The median number of courses was 6.0 (range, 3–20), corresponding to about 6 months of treatment, and sufficient dose intensity could be obtained (31,32). In about 50% of patients, the duration of a treatment cycle was 5 and not 4 weeks because the off period was 3 rather than 2 weeks (data not shown).

The follow-up rate was 78.1% at 36 months. Total PFS and total OS rates were divided each other as follows: 12M-PFS 31.7%, 24M-PFS 12.3%, and 36M-PFS 6.2% (MST: 7.6 M; 95% CI: 6.6–8.5 M) (*Figure 2A*). 12M-OS 70.6%, 24M-OS 49.4%, and 36M-OS 32.1% (MST 22.1 M; 95% CI: 9.2–35.0 M) (*Figure 2B*). Moreover, these groups divided into two groups located in the Rt. sided group and Lt. sided group as follows: 12M-PFS; Rt. 9.1% *vs.* Lt. 40.0% (P=0.037), 24M-PFS; Rt. 0.0% *vs.* Lt. 17.0% (P=0.016), and 36M-PFS; Rt. 0.0% *vs.* Lt. 8.5% (P=0.016)

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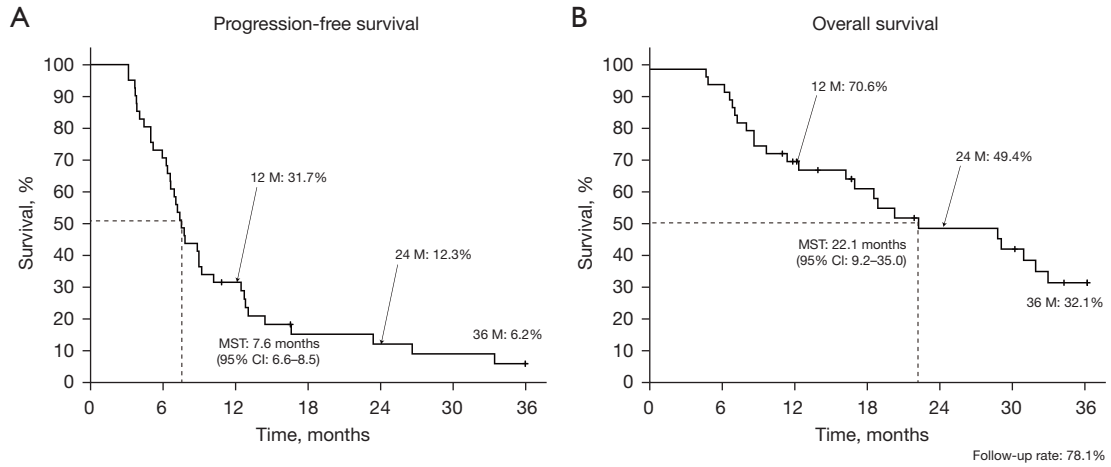
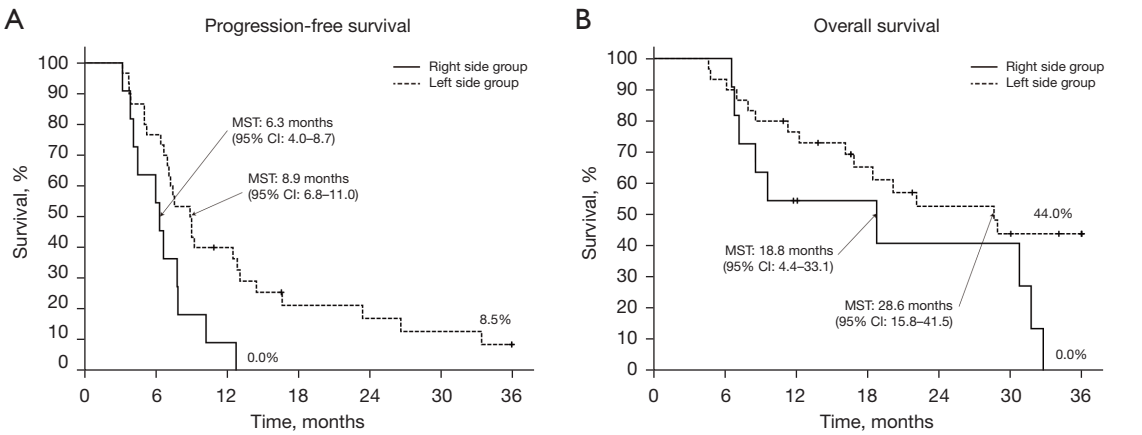


Figure 2 Kaplan-Meyer curves. (A) 12M-PFS: 31.7%, 24M-PFS: 12.3%, and 36M-PFS: 6.2% (MST: 7.6 M). (B) 12M-OS: 70.6%, 24M-OS: 49.4%, and 36M-OS: 32.1% (MST: 22.1 M). The follow-up rate was 78.1%. PFS, progression-free survival; MST, median survival time; OS, overall survival.



Progression-free survival	Right side group (n=11)		Left side group (n=30)		P value
	Survival rate (%)	Hazard ratio (95% CI)	Survival rate (%)	Hazard ratio (95% CI)	
12 months	9.1	Reference	40.0	0.436 (0.199–0.953)	0.037
24 months	0.0		17.0	0.396 (0.186–0.842)	0.016
36 months	0.0		8.5	0.396 (0.186–0.842)	0.016

Overall survival	Right side group (n=11)		Left side group (n=30)		P value
	Survival rate (%)	Hazard ratio (95% CI)	Survival rate (%)	Hazard ratio (95% CI)	
12 months	54.5	Reference	76.5	0.475 (0.150–1.499)	0.204
24 months	40.9		52.7	0.635 (0.240–1.679)	0.360
36 months	0.0		44.0	0.463 (0.201–1.066)	0.070

Figure 3 Kaplan-Meyer curves. (A) 12M-PFS: Rt. 9.1% *vs.* Lt. 40.0% (P=0.037); 24M-PFS: Rt. 0.0% *vs.* Lt. 17.0% (P=0.016); and 36M-PFS: Rt. 0.0% *vs.* Lt. 8.5% (P=0.016) (MST: Rt. 6.3 M/Lt. 8.9 M). (B) 12M-OS: Rt. 54.5% *vs.* Lt. 76.5% (P=0.204); 24M-OS: Rt. 40.9% *vs.* Lt. 52.7% (P=0.360); and 36M-OS: Rt. 0.0% *vs.* Lt. 44.0% (P=0.070) (MST: Rt. 18.8 M/Lt. 28.6 M). PFS, progression-free survival; MST, median survival time; OS, overall survival.

(*Figure 3A*). 12M-OS: Rt. 54.5% *vs.* Lt. 76.5% (P=0.204); 24M-OS: Rt. 40.9% *vs.* Lt. 52.7% (P=0.360), and 36M-OS: Rt. 0.0% *vs.* Lt. 44.0% (P=0.070) (*Figure 3B*).

The most common objective tumor response was SD, followed by PR and PD; no patient achieved CR. The objective tumor response is those of 10 patients (24.4%) and CBR is 31 patients (75.6%) (*Table 3*). The dose was reduced in totally 4 patients (9.8%) only, and the dose interval was prolonged in 19 patients (46.3%) with 12 patients in the left sided colon and 7 patients in the right. According to the results of ORR (Lt. 9 patients *vs.* Rt. 1 patient) and CBR (Lt. 25 patients *vs.* Rt. 6 patients) of each group, the left

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sided group is better results than right sided group (P=0.098) (*Table 4*).

Safety

AEs were as follows: malaise was the most common AE (36.6% of patients), followed by anorexia (29.3%), acne-like rash (29.3%), and diarrhea (26.8%) and stomatitis (24.4%) (*Table 5*). Most AEs were grade 1 or 2 and improved with conservative treatment. Only 10 AEs were grade 3. All these AEs resolved with conservative management. No treatment-related deaths occurred among the patients. The majorities of grade 2-3 AEs are found in the left sided group (*Table 6*).

We also examined in detail the AEs in patients with data on UGT1A1 polymorphism type. Among the 4 patients with *6 heterozygous type, 2 had grade 1 malaise and diarrhea; 1 each had grade 1 anorexia, peripheral sensory neuropathy, and oral mucositis; and 1 patient each had grade 3 leukopenia, neutropenia, and perforation. Among the 3 patients with *28 heterozygous type, 2 had grade 1 anorexia and peripheral sensory neuropathy; 1 each had grade 1 malaise, diarrhea, and oral mucositis; and 1 patient had grade 2 thrombocytopenia. And the patient with *6/*28 double heterozygous type had grade 1 nausea.

A total of 40 patients (97.6%) were suitable for outpatient treatment (performance status, 0–2). One patient received only initial treatment at hospital admission and was then treated as an outpatient. One patient had to be admitted for treatment of leukopenia with a leukocyte-promoting agent. Another patient had to be hospitalized for treatment of severe perforation due to ascending colon cancer with peritoneal dissemination (the patient had previously received bypass surgery for peritoneal dissemination, and the perforation was not caused by chemotherapy but by cancer infiltration as a result of peritoneal dissemination); after drainage, the patient improved and was discharged.

Table 3 Objective tumor response to treatment with modified IRIS (irinotecan plus tegafur/gimeracil/oteracil) with molecular targeting agents

Tumor response	All (n=41)	Dose reduction (n=4, 9.8%)	Dose-interval prolongation (n=19, 46.3%)
Response, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	10 (24.4)	2 (50.0)	15 (36.6)
SD	21 (51.2)	2 (50.0)	9 (47.4)
PD	10 (24.4)	0 (0.0)	5 (26.3)
ORR, n (%)[†]	10 (24.4)	2 (50.0)	15 (36.6)
CBR, n (%)[‡]	31 (75.6)	3 (75.0)	13 (68.4)

[†], defined as CR + PR; [‡], defined as CR + PR + SD ≥6 months. IRIS, irinotecan plus S-1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; CBR, clinical benefit rate.

Discussion

This retrospective analysis found that standardized

Table 4 Comparison of objective tumor response with location of the tumor

Tumor response	Total cases (n=41)	Right side[†] group (n=11)	Left side[†] group (n=30)	P value
Dose reduction	4	0	4	0.559
Dose-interval prolongation	19	7	12	0.290
Response, n				0.150
CR	0	0	0	
PR	10	1	9	
SD	21	5	16	
PD	10	5	5	
ORR, n[‡]	10	1	9	0.238
CBR, n[§]	31	6	25	0.098

[†], location of the primary tumor side; [‡], defined as CR + PR; [§], defined as CR + PR + SD ≥6 months. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; CBR, clinical benefit rate.

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Table 5 Grading of adverse events by the Common Terminology Criteria of Adverse Events, version 5.0

Adverse event	Grade (CTCAE ver. 5.0)		
	Grade 1	Grade 2	Grade 3
Leukopenia, n (%)	3 (7.3)	3 (7.3)	2 (4.9)
Neutropenia, n (%)	1 (2.4)	1 (2.4)	4 (9.8)
Thrombocytopenia, n (%)	1 (2.4)	2 (4.9)	0 (0.0)
Malaise, n (%)	12 (29.3)	2 (4.9)	1 (2.4)
Nausea, n (%)	8 (19.5)	0 (0.0)	1 (2.4)
Anorexia, n (%)	9 (21.9)	3 (7.3)	0 (0.0)
Diarrhea, n (%)	10 (24.4)	0 (0.0)	1 (2.4)
Mucositis oral, n (%)	10 (24.4)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy, n (%)	10 (24.4)	0 (0.0)	0 (0.0)
Rash acneiform, n (%)	10 (24.4)	2 (4.9)	0 (0.0)
Hand foot syndrome, n (%)	1 (2.4)	0 (0.0)	0 (0.0)
Bleeding/perforation, n (%)	0 (0.0)	0 (0.0)	1 (2.4)

CTCAE, Common Terminology Criteria of Adverse Event.

Table 6 Grading of adverse events for location of tumor by the Common Terminology Criteria of Adverse Events, version 5.0

Adverse event (grade 2–3)[‡]	Total cases (n=41)	Right side[†] group (n=11)	Left side[†] group (n=30)
Leukopenia, n	5	1	4
Neutropenia, n	5	2	3
Thrombocytopenia, n	2	0	2
Malaise, n	3	1	2
Nausea, n	1	1	0
Anorexia, n	3	0	3
Diarrhea, n	1	0	1
Mucositis oral, n	0	0	0
Peripheral sensory neuropathy, n	0	0	0
Rash acneiform, n	2	0	2
Hand foot syndrome, n	0	0	0
Bleeding/perforation, n	1	0	1

[†], location of the primary tumor side; [‡], CTCAE, Common Terminology Criteria of Adverse Event (CTCAE ver. 5.0).

second-line chemotherapy with MTA (EGFR or VEGF inhibitor) plus IRIS in patients with advanced recurrent or nonresectable colorectal cancer is associated with good PFS and OS and causes few serious AEs. The left-sided group had better results with longer PFS and longer OS than the right-sided group. Side effects tended to be fewer in the right-sided group, but all cases could be handled with conservative management. Curative radical resection in which a large circular area is removed from the vessel base area was long the accepted first-line therapy for stage I to III colorectal cancer in both Japan (surgical approach: radical D3 lymph node dissection) and Western countries

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(surgical approach: central vascular ligation and complete or total mesocolic) (33,34). However, in recent years, many studies have demonstrated the effectiveness of ICIs as first- and second-line cancer therapy, and the systemic and local immune environment and host relationship have received much attention (13). Pembrolizumab became available as second-line therapy for stage IV colorectal cancer with high MSI January 2019 and was subsequently approved as a first-line therapy in January 2022. In tumor immune environments, many lymphatic lineage cells are present in bone marrow and systemic blood vessels, interstitial spaces, and lymph nodes. Accordingly, when the primary tumor is resected in patients with stage IV colorectal cancer, surgeons must carefully evaluate whether conventional prophylactic complete dissection and resection of lymph nodes near the cancer lesion are necessary. Moreover, minimally invasive laparoscopic surgery should be used for integrated treatment of stage IV colorectal cancer by tumor volume reduction or cyto-reductive R0 surgery because it minimizes complications. ICIs or conventional anti-cancer drugs should be used shortly after surgery, but care should be taken to avoid immunosuppression or bone marrow suppression (29). Thus, we reported the first-line therapy with dose adjusted for the Japanese/Asian population (23). Now, we present the result of 2nd line multi-modality chemotherapy therapy for colorectal cancer.

Petrelli *et al.* reported in 2017 that the prognosis of colorectal cancer is related to its location (35). The prognosis of tumors in the left-sided colon is reported to be better than right-sided colon tumors. For left-sided colon, it is known that cetuximab, anti-EGFR, is more effective, and further research is ongoing for biologics. In this study, approximately 70% of patients were in the left-sided group; first line therapy was CAPOX-Bmab, and the second line therapy was IRIS-Pmab. The outcomes were comparable to those that were reported elsewhere.

The RAS status has been reported to be wild type in approximately 60% to 70% of cases. In the present study, fewer than half the patients (41.5%) were wild-type RAS status (36). Previous studies were mostly in Western populations, and research has indicated that the proportion of people with wild-type RAS status is lower in Japanese and Asian populations, suggesting ethnic differences. Further data are needed to clarify this issue (37). The Japanese health insurance covered RAS assay in 2015 while BRAF assay was covered in 2018. Accordingly, all patients underwent RAS assay in this study, but the BRAF assay was conducted in 24/41 patients (58.5%). Thus, there were differences in the proportion of patients who received these assays.

In the present study, the mutated type UGT1A1 polymorphism was present in about one fifth of patients who underwent this test. Other studies have reported percentages of 10% or less. However, as discussed above, the mutated type may be more common in Japanese and Asian populations. It is reported that among the Asian population, UGT1A1 *6 is about 30%, and *28 about 15%. The incidence was lower in this study (38). The incidence rate of serious AEs was low, so the safety profile of the modified IRIS regimen is considered to be favorable in the patients overall and in all UGT1A1 polymorphism subtypes. Because our modified IRIS regimen uses a lower dose than is used in Western populations, we were expecting that patients would experience mostly low-grade AEs. Furthermore, after UGT1A1 polymorphism testing, all 8 patients with heterozygous type were started on a lower dose of irinotecan, which might also have contributed to the lower grades of AEs. A lower incidence of AEs might lead to a higher rate of treatment continuation, but this topic requires further study. In this study, AEs overall were mild (i.e., grade 1 or 2), and only 10 events occurred that were grade 3 or higher (neutropenia, 4 patients; leukopenia, 2 patients; malaise, 1 patient; nausea, 1 patient; diarrhea, 1 patient; and perforation, 1 patient).

Although we used a lower dose treatment regimen, we were still able to achieve a good objective tumor response (ORR, 24.4%; CBR, 75.6%). These efficacy results indicate that our regimen was not underdosed or underpowered but comparable to or even better than the standard Western dose, as supported by good PFS and OS percentages. The IRIS regimen previously reported in Japan used irinotecan at 125 mg/m^2 (4-week regimen), 100 mg/m^2 (4-week regimen), or 150 mg/m^2 (3-week regimen). However, for the reasons mentioned in the Methods section, we used a modified IRIS plus MTA regimen in which the irinotecan dose was 85 mg/m^2. In this study, the dose reduction rate of irinotecan was only 9.8%, indicating that the dose had to be reduced in only a few patients because of a serious AE.

About 50% of the patients were treated with a dose of 2 weeks/2 weeks off, but in the remaining patients, the off period was extended by an additional 1 week. This longer off period is assumed to improve patient quality of life, this topic warrants further investigation in a future study.

Direct comparison of our findings with those of other

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studies on second-line IRIS therapy in Japan is difficult because of differences in MTA treatment. Nevertheless, our study found a better median PFS (7.6 months) and OS (22.1 months) than 2 other studies in Japan: Takaoka *et al.* reported a median PFS and OS of 9.5 and 20.1 months, respectively, with irinotecan (100 mg/m^2) plus P-mab (25), and Miyamoto *et al.*, a median PFS and OS of 5.6 months and 16.4 months, respectively, with irinotecan (150 mg/m^2) + B-mab (26). In these studies, the location of a tumor has not been investigated. In this study, PFS/OS MST in the right-sided and left-sided groups was 6.3/18.8 months and 8.9/28.6 months, respectively. Although the prognosis is generally poor in the right-sided group, it was favorable in this study. A poor prognosis in the right-sided group is already reported, and remote metastases were more commonly observed in the right-sided group at the initial visit [8/11 patients (72.7%)] than in the left-sided group [16/30 patients (53.3%)]. We observed only 10 AEs of grade 3 or higher (41 cases), whereas Takaoka *et al.* observed 43 such AEs (36 cases) (25) and Miyamoto *et al.*, 63 such events (36 cases) (26). We assume that fewer AEs of grade 3 or higher occurred in the current study than in the other two studies because we used a lower irinotecan dose.

The most common site of colorectal cancer in Japan is the rectum, followed by the sigmoid colon. These anatomical sites occupy approximately 70% of colorectal cancer. Together with the descending colon, left-sided colon comprises approximately 75% of colorectal cancers. The incidence in this study was comparable and was consistent with that of colorectal cancer in Japanese patients. The limitation of this study is that the number of patients in the right-sided group was 11, and smaller than the left-sided group. Because of this, statistical investigation was difficult. Therefore, we will further increase the number of patients to conduct a robust assessment.

Conclusions

To our knowledge, this is the first report on second-line therapy with a modified IRIS regimen comprising minimal chemotherapy doses performed at a single center with a variety of MTAs. The results suggest that, for stage IV recurrent or nonresectable colorectal cancer, second-line therapy with IRIS and MTA shows good efficacy and safety.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-899/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Chemotherapy Committee at Tokai University Hachioji Hospital and the institutional review board for clinical research of Tokai University Medical School (No. 22R-023), and informed consent was taken from all the patients.

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