Original Study

Safety and Efficacy of Trifluridine/Tipiracil Monotherapy in Clinical Practice for Patients With Metastatic Colorectal Cancer: Experience at a Single Institution

Daisuke Kotani,[1] Kohei Shitara,[1] Akihito Kawazoe,[1] Shota Fukuoka,[1] Yasutoshi Kuboki,[1] Hideaki Bando,[1] Wataru Okamoto,[1] Takashi Kojima,[1] Toshihiko Doi,[1] Atsushi Ohtsu,[2] Takayuki Yoshino[1]

Abstract

Little information is available regarding the safety and efficacy of trifluridine/tipiracil (TAS-102) monotherapy in clinical practice. A retrospective study of 55 patients at a single institution was performed to clarify the safety and efficacy of TAS-102 monotherapy in clinical practice. Our findings indicate that the safety and efficacy of TAS-102 seen in pivotal trials are maintained in clinical practice, regardless of the previous use of regorafenib.

Background: The combination drug TAS-102 is a novel oral nucleoside antitumor agent containing trifluridine and tipiracil hydrochloride, which prevents the degradation of trifluridine. The global phase III RECOURSE trial (Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) demonstrated that TAS-102 prolonged the survival of patients with metastatic colorectal cancer (mCRC) whose disease progressed after standard therapies. TAS-102 was first approved in Japan in March 2014, and little is known about its safety and efficacy in clinical practice, especially for mCRC patients with previous regorafenib treatment. **Patients and Methods:** We investigated the safety and efficacy of TAS-102 monotherapy in clinical practice for patients with mCRC refractory to standard therapies who were treated from May 2014 to January 2015. **Results:** A total of 55 patients received TAS-102. The Eastern Cooperative Oncology Group performance status was 0, 1, and 2 in 41.8%, 47.3%, and 10.9% of patients. Of the 55 patients, 32 (58.2%) had been treated with regorafenib before receiving TAS-102. The median progression-free survival and overall survival was 2.0 months and 5.3 months, respectively. Emergency hospitalization was required for 23.6% of the patients during TAS-102 treatment, although most of the events (76.9%) were disease-related. The most common grade 3 or 4 adverse events were neutropenia (41.8%), leukopenia (27.2%), anemia (23.6%), febrile neutropenia (5.5%), and fatigue (3.6%). The frequency of grade $\geq$ 3 events was not significantly increased among the patients who had compared with those who had not received regorafenib. The progression-free survival (median 2.1 vs. 2.0 months) and overall survival (median 6.2 vs. 4.7 months) were similar for the 2 subgroups. **Conclusion:** The safety and efficacy of TAS-102 monotherapy in clinical practice were maintained, irrespective of previous regorafenib treatment.

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Introduction

Colorectal cancer is the third most common cancer and the fourth leading cause of cancer death worldwide.[1] The development of combination chemotherapy regimens with cytotoxic drugs (eg, oxaliplatin, irinotecan, and fluoropyrimidine) and molecular targeting agents (eg, bevacizumab, aflibercept, cetuximab, panitumumab, and

[1]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan
[2]Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Chiba, Japan

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Address for correspondence: Kohei Shitara, MD, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
E-mail contact: kouheis0824@yahoo.co.jp

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regorafenib) has prolonged the survival time of patients with metastatic colorectal cancer (mCRC).[2-10] Thus, the median overall survival (OS) has reached approximately 30 months in a clinical trial setting for mCRC.[11] However, effective treatments for patients with mCRC refractory or intolerant to these anticancer agents are still limited, although many patients long maintain good performance status (PS).

TAS-102 is a novel oral nucleoside antitumor agent containing trifluridine and tipiracil hydrochloride, which prevents the degradation of trifluridine.[12] TAS-102 was first approved in Japan in March 2014, and the safety of TAS-102 with the Japanese recommended dose was also confirmed in Western patients.[13-15] In a global phase III RECOURSE trial (Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies), 800 patients with mCRC refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab, and anti-epidermal growth factor receptor antibodies of wild-type KRAS were randomly assigned in a 2:1 ratio to either TAS-102 (35 mg/m^2 per dose twice daily on days 1 to 5 and 8 to 12, every 4 weeks) or placebo. Treatment with TAS-102 resulted in a significantly longer OS (median, 7.1 vs. 5.3 months; hazard ratio [HR], 0.68; $P < .0001$), significantly longer progression-free survival (PFS; median, 2.0 vs. 1.7 months; HR, 0.48; $P < .0001$), and significantly greater disease control rate (DCR; 44.0% vs. 16.3%; $P < .0001$) compared with placebo. The common adverse events with TAS-102 were leukopenia, neutropenia, anemia, and thrombocytopenia.[16] Although TAS-102 was well tolerated, the proportion of patients with previous regorafenib treatment was only 17% in the TAS-102 group, which consisted of a non-Asian population. Also, patients with Eastern Cooperative Oncology Group (ECOG) PS 2 were not eligible for the RECOURSE study. Thus, the safety profile and efficacy for patients with previous regorafenib treatment or poor PS status remain unknown.

The results from clinical trials do not always reflect those in clinical practice, although randomized controlled trials provide the highest level of evidence. TAS-102 for mCRC was approved first in Japan, ahead of the approval in other countries, in March 2014 and little is known about its safety and efficacy in clinical practice worldwide. We accordingly retrospectively investigated the characteristics and clinical outcomes of patients with mCRC who had been treated with TAS-102 in clinical practice at our institution, including the safety and efficacy of TAS-102 with or without previous regorafenib treatment.

Patients and Methods

We reviewed the clinical records of patients with mCRC who had been treated with TAS-102 after standard therapies at our institution from May 2014 to January 2015. All patients had presented with histologically confirmed colorectal adenocarcinoma. The retrospective study was conducted under an institutional review board waiver in accordance with the Japanese Ethical Guidelines for Epidemiological Research.

The baseline characteristics were collected for each patient as follows: age, sex, tumor histologic type, ECOG PS, primary site, site of metastasis, number and regimen of previous treatments, time from the start of systemic chemotherapy, and status of KRAS exon 2, 3, and 4 and NRAS exon 2, 3, and 4, if available.

The dose intensity was defined as the cumulative dose (mg/m^2) divided by the number of weeks from initial treatment to discontinuation or the cutoff date. The relative dose intensity was defined as the dose intensity (mg/m^2 per week) divided by the regulated dose (175 mg/m^2 per week), similar to the dose used in the TAS-102 pivotal clinical trials.[13,14]

Table 1 Patient Characteristics (n = 55)

Characteristic	Value	Previous Regorafenib	
		Yes (n = 32)	No (n = 23)
Age (years)			
Median	66	66	66
Range	38-78	38-78	41-78
Sex			
Male	27 (49.1)	15 (46.9)	12 (52.2)
Female	28 (50.9)	17 (53.1)	11 (47.8)
ECOG PS			
0	23 (41.8)	14 (43.8)	9 (39.1)
1	26 (47.3)	16 (50.0)	10 (43.5)
2	6 (10.9)	2 (6.2)	4 (17.4)
Primary site			
Right side colon	14 (25.4)	9 (28.1)	5 (21.7)
Left side colon	15 (27.3)	6 (18.8)	9 (39.1)
Rectum	26 (47.3)	17 (53.1)	9 (39.1)
Metastatic organs (n)			
1	7 (12.7)	5 (15.6)	2 (8.7)
2	18 (32.7)	8 (25.0)	10 (43.5)
≥3	30 (54.5)	19 (59.4)	11 (47.8)
Time from start of systemic chemotherapy (mo)			
<18	17 (30.9)	12 (37.5)	5 (21.7)
≥18	38 (69.1)	20 (62.5)	18 (78.3)
KRAS exon 2 status			
Wild-type	33 (60.0)	17 (53.1)	16 (69.6)
Mutant-type	22 (40.0)	15 (46.9)	7 (30.4)
All RAS status			
Wild-type	26 (47.3)	14 (43.8)	12 (52.2)
Mutant-type	24 (43.6)	15 (46.9)	9 (39.1)
Unknown	5 (9.1)	3 (9.4)	2 (8.7)
Previous regimens (n)			
1-2	15 (27.3)	1 (3.1)	14 (60.9)
3	24 (43.6)	16 (50.0)	8 (34.8)
≥4	16 (29.1)	15 (46.9)	1 (4.3)
Previous chemotherapy agents			
Fluoropyrimidine	55 (100)	32 (100)	23 (100)
Irinotecan	52 (94.5)	30 (93.8)	22 (95.7)
Oxaliplatin	54 (97.6)	32 (100)	22 (95.7)
Bevacizumab	54 (97.6)	32 (100)	22 (95.7)
Anti-EGFR mAb	27 (49.1)	16 (50.0)	11 (47.8)
Regorafenib	32 (58.2)	32 (100)	0

Data presented as n (%), unless noted otherwise.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; PS = performance status.