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TRIAL PROTOCOL

A Trial Protocol of Biweekly TAS-102 and Bevacizumab as Third-Line Chemotherapy for Advanced/Recurrent Colorectal Cancer: A Phase II Multicenter Clinical Trial (The TAS-CC4 Study)

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Abstract:

Background: Treatment with TAS-102 has significantly improved the progression-free survival (PFS) and overall survival (OS) of patients with metastatic colorectal cancer (mCRC). Reportedly, the combination of TAS-102 plus bevacizumab extends the median PFS. The present study aimed to confirm the efficacy and safety of TAS-102 plus bevacizumab (biweekly administration) as third-line chemotherapy for patients with mCRC. Methods/Design: This is a single-arm, open-label, prospective, nonrandomized, multicenter phase II trial conducted in Japan. With a threshold and expected PFS of 2.1 and 3.5 months, respectively, the simulation results showed a sample size of 42 with $\alpha = 0.05$ (both sides) for 90% power, based on the One-Arm Binomial test using the SWOG statistical tool. If the estimated dropout is 7%-8%, the target sample size is estimated to be 45. The TAS-CC4 study regimen comprised 28-day cycles with biweekly oral administration of TAS-102 (35 mg/m^2 twice daily on days 1-5 and 15-19 of every 28-day cycle) and bevacizumab (5.0 mg/kg on days 1 and 15). The primary end point is the PFS; secondary end points include response rate (RR), OS, grade ≥3 neutropenia, and genetic alterations (KRAS/BRAF mutations) in the circulating cell-free DNA. Discussion: The present study can contribute to the determination of the effective dosing interval of TAS-102 and bevacizumab in patients with mCRC and is thought to lead to prophylaxis of neutropenia and prolongation of the treatment period.

Keywords:

colorectal cancer, TAS-102, biweekly administration, neutropenia

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Background

TAS-102 is an oral anticancer agent composed of trifluridine (FTD) and tipiracil hydrochloride[1]. Mechanistically, FTD incorporates into the DNA of colorectal cancer (CRC) cells to exert its antitumor effect[2], whereas tipiracil hydrochloride maintains blood concentration of FTD by inhibiting the FTD-degrading enzyme thymidine phosphorylase. In the global phase III RECOURSE trial, progression-free survival (PFS) and overall survival (OS) were significantly better in patients with CRC treated with TAS-102 than those treated with a placebo. However, grade ≥3 neutropenia (38%) was frequently observed in patients treated with TAS-102[3]. Furthermore, combination chemotherapy of TAS-102 plus bevacizumab was reportedly associated with grade ≥3 neutropenia in 72% of treated patients[4]. Neutropenia is the most common adverse event associated with chemotherapy[5,6] and an important factor affecting chemotherapy continuation[7]. Thus, overcoming neutropenia is assumed to improve survival rates. We previously reported a case of a patient in whom neutropenia was avoided by altering the TAS-102 administration protocol[8]. Given the success of this case, it was necessary for us to investigate whether neutropenia could be suppressed by altering the TAS-102 administration protocol in other patients. Subsequently, we reported a retrospective analysis concerning the administration protocol suppressing neutropenia, without changing the drug dose intensity[9]. However, to the best of our knowledge, there have been no prospective reports regarding the administration of TAS-102 aimed at reducing neutropenia. The main purpose of the present study is to estimate the efficacy and safety of biweekly administration of TAS-102 plus bevacizumab as third-line chemotherapy for patients with unresectable and recurrent CRC.

Methods/Design

The present study is designed as a prospective, nonrandomized, single-arm, multi-centered open-label phase II trial. Patients will be recruited in 12 centers in Japan. Written informed consent (IC) will be obtained by investigators from the patient prior to any screening or inclusion procedures. The trial is organized by the Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan.

Study schedule

The present study was registered as UMIN000030030 on November 18, 2017. The trial started on December 2017. The estimated study completion date is 2020 (final data collection, date for primary outcome measurement). Survival status will be collected for 1 year after registration.

Sample size analysis

The RECOURSE trial was referred for calculating sample size[3]. In the study, the PFS was 2.0 months. With a threshold and expected PFS of 2.1 and 3.5 months, respectively, the simulation results indicated a sample size of 42 with $\alpha = 0.05$ (both sides) for 90% power based on the One-Arm Binomial test using the SWOG statistical tool. If the estimated dropout is 7%-8%, a target sample size of 45 is estimated.

Patient selection criteria

Inclusion criteria

1. With unresectable advanced, metastatic, or recurrent CRC that has been pathologically diagnosed as adenocarcinoma
2. With previous administration of first- and second-line chemotherapy for metastatic CRC and tumors diagnosed as progression of disease (PD)
3. Aged between 20 and 80 years
4. With an Eastern Cooperative Oncology Group Performance Status of 0 or 1
5. With measurable lesions based on the Response Evaluation Criteria in Solid Tumors version 1.1
6. Able to take oral medication
7. With a life expectancy of at least 3 months
8. Exhibiting sufficient organ function for up to 2 weeks prior to enrollment in the study with the following parameters considered:
   - Leukocyte count ≥ 3,500/mm^3
   - Absolute neutrophil count ≥ 1,500/mm^3
   - Hemoglobin level ≥ 8.0 g/dL
   - Platelet count ≥ 75,000/mm^3
   - Total bilirubin level ≤ 1.5 mg/dL
   - Aspartate aminotransferase level ≤ 2.5 × upper limit of normal
   - Alanine aminotransferase level ≤ 2.5 × upper limit of normal
   - Serum creatinine level ≤ 1.5 mg/dL
   - Peripheral neuropathy ≤ grade 2
   - No active infectious disease
   - No recognizable diarrhea or non-hematological adverse events (except for alopecia, dysgeusia, and pigmentation)
9. Providing signed written IC prior to enrollment in the present study

Exclusion criteria

1. History of severe drug allergy
2. History of treatment with TAS-102
3. Severe liver dysfunction
4. Females who are pregnant or planning a pregnancy and males intending to impregnate their partner
5. Uncontrollable hypertension (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg,

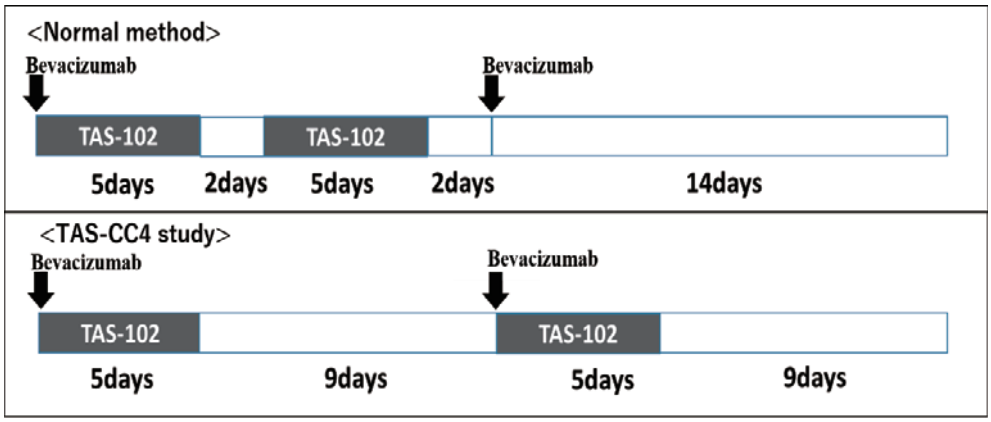

Figure 1. Administration protocol for the study.

even when taking oral antihypertensives)
6. Other serious complications (symptomatic unstable ischemic heart disease, arrhythmia, interstitial pneumonia, pulmonary fibrosis, renal failure, liver failure, uncontrollable diabetes mellitus, and gastrointestinal ulcers)
7. Presence of other active cancers
8. Clinical or radiological evidence of brain metastases
9. Current ongoing treatment with corticosteroids
10. Any other criteria for which the investigator deems patients unsuitable for the present study
11. Contraindications for TAS-102 and Bevacizumab
12. Proteinuria ≥ grade 2
13. Gastrointestinal ulcer or bleeding
14. Previous hemoptysis
15. Ongoing treatment with anticoagulant
16. Synchronous or metachronous multiple malignancy within the last 5-year disease-free interval

Treatment

The TAS-CC4 study regimen consists of 28-day cycles with biweekly administration of TAS-102 (orally administered at a dose of 35 mg/m^2 twice daily on days 1-5 and 15-19 of every 28-day cycle) plus bevacizumab (5.0 mg/kg on days 1 and 15) (Figure 1). In the present study, a treatment schedule, in which TAS-102 is administered for 5 consecutive days, followed by 9 days without treatment, is adopted.

Treatment was continued until any of the following occurred: progressive disease, consent withdrawal, unacceptable toxicity, discontinuation based on clinical indications, or the investigator's discretion. Other chemotherapy, radiotherapy, immunotherapy, hormone therapy, hyperthermia, and prophylactic administration of G-CSF are prohibited during the trial.

Criteria for suspending and resuming drug administration

Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE ver. 4.0). When neutropenia, thrombocytopenia, or hypertension were recognized, drug administration was suspended and resumed based on appropriate criteria. If other adverse events reached grade ≥3, drug administration was suspended until improvement to a grade ≤2 and then resumed with a 10-mg reduction in the TAS-102 dose. In addition, attending physicians suspended or discontinued drug administration when deemed appropriate.

Objectives

1) Primary end point
- PFS

2) Secondary end point
- Incidence of neutropenia ≥ grade 2
- Time to treatment failure (TTF)
- Response rate
- OS
- Mutation effects
- RAS in circulating cell-free DNA on prognosis

3) Safety evaluation
- Incidences of adverse events ≥ grade 3

Observation and examination contents

1) Patients' characteristics: gender, performance status, medical history, comorbidity, allergy, and blood pressure
2) Tumor characteristics: previous treatments, primary/recurrent, histological findings, clinical stage, and RAS mutation status
3) Radiological findings: computed tomography and magnetic resonance imaging
4) Blood examination: white blood cell (WBC), neutrophils, and platelet count and hemoglobin, AST, ALT, total bilirubin, LDH, creatinine clearance (CCr), and electrolyte level
5) Tumor markers: CEA and CA19-9

Cell-free DNA extraction

Blood samples were collected before and after chemotherapy. The samples were transferred in cell-free DNA BCT tubes (Streck, Omaha, NE). Blood was centrifuged at 1,900 g for 10 min at 4°C to separate the plasma from the peripheral blood cells and stored at −80°C until cell-free DNA extraction. After re-centrifugation at 16,000 g for 10 min at 4°C to remove debris, cell-free DNA was extracted from 1,000 μL of plasma into 30 μL of elution buffer using a Maxwell® RSC cfDNA Plasma Kit (Promega, Madison, WI, USA).

Translational genomic analysis

Genetic alterations (KRAS, NRAS, and BRAF mutations) were studied by analyzing the circulating cell-free DNA, which was then obtained both prior to the initiation of and during the chemotherapy. All KRAS, NRAS, and BRAF mutations detected from each sample were investigated using digital PCR (QuantStudio 3D Instrument, Thermo Fisher Scientific). The resulting data are reported in copies/μL together with the results of the data quality assessment metrics. To analyze the data deeper, QuantStudio 3D Analysis Suite Cloud Software (Thermo Fisher Scientific) was used for quantitative and relative data analysis. The correlations between genetic alterations over time and patient outcomes or responses to TAS-102 plus bevacizumab chemotherapy were evaluated.

Data collection

The researchers at each hospital maintained individual records for each patient as source data, including a copy of medical records, IC, image data, laboratory data, and other records. All of the data were collected by the Nippon Medical School Data Center. The data center oversaw the data sharing process within the trial. Clinical data entry, central monitoring, and data management were performed. Interim analysis and auditing were not planned for the study.

Data monitoring

Central data monitoring reports were compiled twice a year by the data managers and reported to the principal and site investigators. According to the procedure manual of the present study, the monitoring was conducted. An independent data monitoring committee was established to confirm safety data in the event of serious adverse events. The responsible person was Dr. Yoshikazu Kanazawa (Associate Professor, Nippon Medical School) who is not a coauthor of the present study.

Serious adverse events were reported to the institutional review board (IRB) of Nippon Medical School (main research establishment) and the safety monitoring board (Tetsuo Shinohara, Department of Surgery, Fukuoka Dental College). Continuance of the study was conferred at the safety monitoring board.

Data access

Only the clinical data managers of Nippon Medical School data center can access the reported case data. Site investigators can access all case data.

Protocol modification

Modifications of the study protocol were communicated to the IRB of each study facility. Each IRB modified the IC materials to be given to participants and adjusted them according to the institution's guidelines.

Confidentiality

Personal data such as medical ID, name, and address were not collected.

Statistical considerations

All patients receiving TAS-102 and bevacizumab chemotherapy were subjected to the analysis. After enrollment, ineligible patients were excluded from the present study. Response rates with 95% confidence intervals were calculated for all eligible patients. The Kaplan-Meier method was used to calculate PFS and OS, and univariate analyzes were performed using the log-rank test. Correlations were analyzed using Spearman's rank correlation coefficient.

Ethical considerations and written IC

The study protocol was approved by the IRB, the Ethics Committee of Nippon Medical School (Tokyo, Japan) on the November 10, 2017 under the registration number 229022. A written IC was obtained from each patient before his/her participating in the study. The appropriate time to notify the patient about the trial was left to the discretion of the medical team. Each researcher was committed to implementing the obligations of the law in accordance with the provisions of the Helsinki Declaration.

Role of the coordinating center in study organization

The coordinating center at Nippon Medical School was responsible for monitoring and management of this multicenter study at all collaborating intuitions. The coordinating center was chosen by mutual agreement among the participating institutions.

Dissemination policy

The results of the present study are submitted for publication in peer-reviewed journals and the important findings are presented at domestic and international conferences.

The authorship is assigned in accordance with the International Committee of Medical Journal Editors guidance.

Discussion

Based on several trials and considering its efficacy and toxicity, 35 mg/m^2 TAS-102 twice daily for 5 days a week for 2 weeks was established as the recommended dose[10-13]. The dose of TAS-102 (35 mg/m^2) in combination with bevacizumab in the present study is based on the results of the C-TASK FORCE trial[4]. Although the current administration protocol was established based on these trials, it remains unclear whether the administration protocol is optimal as only a few administration protocols have been examined.

Tanaka *et al.* reported on the relationship between FTD incorporated into tumor cell DNA and administration duration[14] and showed that FTD uptake into cancer cell DNA increased with increasing administration duration, albeit with worsening efficacy. Their data suggested that the most efficient protocol includes an administration duration of 3-5 days. Conventional protocol is not effective because drug administration is concentrated in the first half of each cycle. Dose intensities in the conventional (TAS-102 on days 1-5 and 8-12 of the 28-day cycle) and biweekly protocols (TAS-102 on days 1-5 and 15-19 of the 28-day cycle) are equal. We suggest that biweekly administration might be beneficial for efficient incorporation of FTD into cancer cell DNA with minimal adverse events.

The doses and concentrations of FTD used and incorporated into the DNA of cancer cells or WBCs are different[15]. Concentrations of FTD in cancer cells were approximately 6 times higher than those in WBCs; therefore, it is possible that the development of novel administration protocols could achieve the maintenance of antitumor effects without bone marrow suppression.

Therefore, the present study may contribute to the determination of the efficacy of the escalation of the administration dose in patients with metastatic colorectal cancer.

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Disclaimer

Takeshi Yamada is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Conflicts of Interest

There are no conflicts of interest.

Source of Funding

All treatments in the present study are covered by national health insurance. The cost of cell-free DNA extraction and translational genomic analysis by digital PCR is funded by the Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School. There are no competing interests between pharmaceutical companies and the investigators with regard to the present study that require disclosure.

Trial registration information

Registry name: TAS-102 and bevacizumab as third-line chemotherapy for colorectal cancer (the TAS-CC4 study)

Trial ID: UMIN000030030.

URL: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000034286

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