Case report

Capcitabine plus bevacizumab as first-line therapy for metastatic colorectal cancer

patients with poor performance status

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Running title: Capcitabine plus Bmab for PS3 patients

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Abstract

Background: Benefit of chemotherapy for patients with metastatic colorectal cancer is well known, however, that for those patients with poor performance status is little known.

Patients and methods: We retrospectively evaluated efficacy of chemotherapy with capecitabine and bevacizumab for patients with poor PS (PS 3).

Results: Seven patients were included and the median age of the patients was 82 years (range, 65–91 years). The response was not ascertained; nonetheless, the disease control rate was 83.3%. The median PFS and OS were 10.0 and 25.8 months, respectively. Hand foot syndrome (HFS) was the most common toxicity observed (three patients: 42.9%). Grade 3 toxicities were found in one patient with proteinuria and one with hypertension.

Conclusion: This limited study indicated that chemotherapy using capecitabine and bevacizumab for patients with poor PS may provide favorable OS and OS. Needless to say, we should be careful not to impose extra burden to patients with poor PS.

Keywords: Capecitabine, bevacizumab, metastatic colorectal cancer, performance status
Introduction

The AVEX study conducted in elderly people over 70 years old showed that the capecitabine + bevacizumab (Bmab) regimen significantly prolonged the progression-free survival (PFS) when compared to capecitabine monotherapy; moreover, it was considered as an effective and tolerable regimen as first-line therapy for elderly patients. However, in the AVEX study, only one patient with poor performance status (PS) was enrolled. Several clinical guidelines deemed the single administration of fluoropyrimidine with or without molecular-targeted drugs as inappropriate for intensive therapy in patients with metastatic colorectal cancer (mCRC). The guidelines for colorectal cancer treatment published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommend a combination therapy of fluoropyrimidine with a molecular-targeted drug for patients who are unfit for chemotherapy. In addition, the capecitabine + Bmab regimen has been used in elderly patients, in those with poor PS, and in those who did not desire aggressive chemotherapy. However, little is known about the benefits of chemotherapy in elderly mCRC patients or those with poor PS. This study aimed to evaluate the effect of capecitabine + Bmab.
therapy for mCRC patients with poor PS.

Patients and methods

Patients

Seven out of 21 patients with mCRC consecutively initiated with capecitabine + Bmab as a first-line chemotherapy from April 2014 to December 2017 at the Department of Surgery, Tokyo Women’s Medical University Medical Center East were enrolled in this study. The general inclusion criteria of this region in the institute are if the assessment of a patient’s clinical condition for chemotherapy is vulnerable or patient’s request. All seven patients presented with Eastern Cooperative Oncology Group (ECOG) PS3. The clinicopathological factors and treatment outcomes were retrospectively analyzed. Written informed consent was obtained from the patients before participation in the study. The protocol of this study was approved by the Review Board (Approved No. 4729-R).

Treatment regimen
Each patient was intravenously injected with Bmab (7.5 mg/kg) on day 1, and advised to take 1000 mg/m² of capecitabine, orally, twice a day for 14 days. This treatment was provided every 3 weeks. Dose modifications of two drugs and the treatment intervals were adjusted by the doctor based on the toxicity and consent of the patient.

Assessment

Computed tomography was performed every 2 or 3 months to evaluate the disease response. The best response during the treatment period was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1⁵), and the toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 4.0⁶). The PFS and overall survival (OS) since the start of the chemotherapy were investigated wherein. The case with conversion therapy was censored.

Statistical analysis

Statistical analyses were performed with JMP Pro 13 (SAS Institute Inc., Cary, NC,
USA). The Kaplan-Meier method was used to estimate the PFS of the first-line regimen and OS. Significant differences were identified by the log-rank test. A $P$-value <0.05 was considered as statistically significant.

**Results**

**Patients’ characteristics**

The characteristics of the enrolled patients are summarized in Table 1. The median age of the patients was 82 years (range, 65–91) and five patients were above 80 years old. The study comprised three males and four females. The colon and rectum were the primary sites of cancer in 5 and 2 patients, respectively. Six patients were histologically diagnosed with differentiated types of tumors: three were classified as N0 based on the Japanese Classification of Colorectal Carcinoma, three as N1, and one as N2. Furthermore, three patients presented with metastasis in the peritoneum and one each in a local site, liver, lung, and bone, respectively.

**Response**

The median number of treated cycles with capecitabine + Bmab was seven (range, 1–17
cycles). No complete or partial response was observed in any of the patients. The best response during treatment was stable disease in five patients. As a result, the disease control rate was 83.3%, excluding patients who failed in one course (Table 2). No improvement in PS was observed in any of the patients during chemotherapy.

Prognosis

The median PFS was 10.0 months (Figure 1). The most common reason for discontinuation of the regimen was disease progression in five patients. The other reasons included a further decrease in PS in one patient and a lack of compliance in another patient (Table 3).

Three patients underwent second-line therapy; one with S-1, irinotecan + Bmab, one with irinotecan + Bmab, and one with trifluridine/tipiracil (TAS102).

The median OS in the enrolled patients was 25.8 months (Figure 2).

Dose intensity

Two out of 7 patients did not perform dose reduction in neither capecitabine nor Bmab. One patient had 25% dose reduction of capecitabine from the start of chemotherapy. The other patient had finally 50% reduction of capecitabine and postpone because of toxicity.
The most patients had extension of rest period. The relative dose intensity for all cases was 69.5% in capecitabine and 68.4% in Bmab.

Adverse drug reaction

The toxicities encountered during the regimen are summarized in Table 4. The most common toxicity, including all grades, was hand foot syndrome (HFS) observed in three patients (42.8%). The most common toxicity with grade 3 or 4 were proteinuria and hypertension detected in two patients (28.6%); one patient with proteinuria and one with hypertension presented with grade 3 toxicities. Owing to the presence of only a few hematological toxicities in this study, the capecitabine + Bmab regimen was considered as well-tolerable. One patient discontinued the treatment after the first course due to a further decrease in the PS as a result of bowel obstruction. None of the patients discontinued the treatment due to toxicities.

Discussion

Although the response rate of the capecitabine + Bmab regimen has been reported to be over 30% \(^8,^9\), no response was observed in any of the patients in the current study.
Furthermore, the disease control rate in the present study was superior to that in the AVEX study and similar to that in the MAX study. In the current study, the median PFS after first-line treatment was 10.0 months for the PS3 patients. Feliu et al. reported a median PFS and OS of 10.8 and 18 months, respectively, in a total of 59 mCRC patients aged ≥70 years, who treated with capcitabine + Bmab as a first-line therapy. The OS in the present study was 25.8 months.

The reason for the good prognosis in the PS3 patients in this study may be due to the absence of multiple organ metastases, which may have resulted in a relatively less tumor burden. Additionally, cases considered resectable if the patients had good PS might be included. Moreover, the basic activities of daily living and nutritional conditions were maintained in some of the patients even during chemotherapy resulting in some patients requiring first-line therapy for a prolonged period. The toxicity in the current study was significantly lower than those reported in previous studies. These findings confirmed that the capcitabine + Bmab regimen as practically tolerable in patients with poor PS.

In conclusion, this study demonstrates the favorable PFS and OS obtained despite the inadequate anti-tumor response in the patients with poor PS. Adverse events were
considered as tolerable due to the occurrence of only a few toxicities. Our findings indicate that capecitabine + Bmab may provide favorable OFS and OS for treatment of vulnerable mCRC patients with poor PS.

Disclosure of conflicts of interest
The authors declare no conflicts of interest associated with this manuscript.

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Figure legend

Figure 1.
Kaplan-Meier curve of time to treatment failure.

Figure 2.
Kaplan-Meier curve of overall survival.
Figure 1

Days after initiation of capecitabine plus Bmab

Survival rate (%)
Figure 2

Survival rate (%) vs. Days after initiation of capecitabine plus Bmab.
| case | Age | Gender | T   | N   | Primary site       | Metastatic site        | CEA  | Alb | CRP | NLR* | Response |
|------|-----|--------|-----|-----|-------------------|------------------------|------|-----|-----|------|----------|
| 1    | 82  | F      | T4a | N2  | T                 | Peritoneal dissemination | 148.4 | 3.5 | 0.52 | 2.43 | SD       |
| 2    | 84  | M      | T3  | N1  | Rb                | Local recurrence        | 6.6  | 3.1 | 1.30 | 4.12 | SD       |
| 3    | 65  | M      | T4a | N0  | RS                | Bone                    | 3.6  | 4.2 | 0.05 | 3.30 | SD       |
| 4    | 91  | F      | T3  | N0  | A                 | Peritoneal dissemination | 4.5  | 3.5 | 0.51 | 1.92 | SD       |
| 5    | 76  | F      | T4b | N1  | S                 | Peritoneal dissemination | 77.3 | 3.2 | 0.27 | 2.48 | PD       |
| 6    | 81  | F      | T3  | N1  | C                 | Liver, Peritoneal dissemination | 9.7  | 3.8 | 0.31 | 5.46 | SD       |
| 7    | 83  | M      | T4a | N0  | T                 | Lung                    | 7.4  | 4.6 | 0.20 | 2.15 | SD       |

*neutrophil-to-lymphocyte ratio
### Table 2. Treatment cycles and response

| Number of treated cycles | 7 (1-27) |
|--------------------------|----------|
| Response                 |          |
| SD                       | 5        |
| PD                       | 1        |
| disease control rate     | 83.3%    |
| Reason                          | Count |
|--------------------------------|-------|
| Disease progression            | 5     |
| Worse performance status       | 1     |
| Patient's desire               | 1     |
| 2nd-line treatment             |       |
| No                             | 5     |
| Yes                            | 3     |
| IRIS + Bmab                    | 1     |
| Irinotecan + Bmab              | 1     |
| TAS102                         | 1     |
Table 4 Adverse events according to National Cancer Institute Common Terminology Criteria for Adverse

|                    | All | G1 | G2 | G3 | G4 | G3/4 (%) |
|-------------------|-----|----|----|----|----|----------|
| All               | 13  | 7  | 5  | 2  | 0  | 2 (15.4) |
| Hematologic toxicities |     |    |    |    |    |          |
| Neutropenia       | 1   | 1  | 0  | 0  | 0  | 0        |
| Non-Hematologic toxicities |     |    |    |    |    |          |
| General fatigue   | 1   | 1  | 0  | 0  | 0  | 0        |
| Mucositis oral    | 1   | 1  | 0  | 0  | 0  | 0        |
| Diarrhea          | 1   | 0  | 0  | 0  | 0  | 0        |
| Hypertension      | 1   | 1  | 0  | 1  | 0  | 1        |
| Hand-foot syndrome| 3   | 0  | 3  | 0  | 0  | 0        |
| Proteinuria       | 1   | 0  | 0  | 1  | 0  | 1        |
| Hemorrhage        | 1   | 1  | 0  | 0  | 0  | 0        |
| Dysgeusia         | 2   | 2  | 0  | 0  | 0  | 0        |
| AST               | 1   | 0  | 1  | 0  | 0  | 0        |