—Case Reports—

Capecitabine Plus Bevacizumab as First-Line Therapy for Patients with Metastatic Colorectal Cancer and Poor Performance Status

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Background: The benefit of chemotherapy for patients with metastatic colorectal cancer has not been established.

Methods: We retrospectively evaluated the effectiveness of chemotherapy with capecitabine and bevacizumab for patients with a performance status (PS) of 3.

Results: Seven patients were included; median age was 82 years (range, 65-91 years). Response was not ascertained; however, the disease control rate was 83.3%. Median PFS and OS were 10.0 and 25.8 months, respectively. Hand-foot syndrome was the most common toxicity observed (3 patients; 42.9%). Grade 3 toxicity was observed in 1 patient with proteinuria and 1 with hypertension.

Conclusion: Chemotherapy using capecitabine and bevacizumab appeared to improve OFS and OS for patients with poor PS. However, care must be taken not to impose unnecessary burdens on patients with poor PS. (J Nippon Med Sch 2021; 88: 496–499)

Key words: capecitabine, bevacizumab, metastatic colorectal cancer, performance status

Introduction

The AVEX study of adults older than 70 years showed that a capecitabine + bevacizumab (Bmab) regimen significantly prolonged progression-free survival (PFS), as compared with capecitabine monotherapy, and was effective and tolerable as first-line therapy for elderly patients[1]. However, that study enrolled only 1 patient with poor performance status (PS). Several clinical guidelines consider single administration of fluoropyrimidine, with or without molecularly targeted drugs, as inappropriate for intensive therapy in patients with metastatic colorectal cancer (mCRC)[2,3].

The guidelines for colorectal cancer treatment of the Japanese Society for Cancer of the Colon and Rectum recommend combination therapy with fluoropyrimidine and a molecularly targeted drug for patients who are unfit for chemotherapy[4]. In addition, the capecitabine + Bmab regimen has been used in elderly patients, in those with poor PS, and in those who decline aggressive chemotherapy. However, the benefits of chemotherapy are unclear for elderly patients with mCRC and those with poor PS. This study evaluated the effects of capecitabine + Bmab therapy for mCRC patients with poor PS.

Patients and Methods

Patients

We enrolled 7 of 21 patients with mCRC consecutively started on capecitabine + Bmab as first-line chemotherapy from April 2014 through December 2017 at the Department of Surgery of Tokyo Women's Medical University Medical Center East. 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 7 patients presented with an Eastern Cooperative Oncology Group (ECOG) PS of 3. Clinicopathological factors and treatment outcomes were retrospectively analyzed. Written informed consent was obtained from all patients before participation in the

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https://doi.org/10.1272/jnms.JNMS.2021_88-415
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Characteristics of Patients

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 treatment cycles		7 (1-27)
Response	SD	5
	PD	1
	Disease control rate	83.3%

study. The protocol of this study was approved by the Review Board of Tokyo Women's Medical University, Tokyo, Japan (Approval No. 4729-R).

Treatment Regimen

Each patient was intravenously injected with Bmab (7.5 mg/kg) on day 1 and advised to take 1,000 mg/m^2 of capecitabine, orally, twice a day for 14 days. This treatment was provided every 3 weeks. The doses of the 2 drugs and treatment intervals were adjusted by the physician in charge on the basis of drug toxicity and the wishes of the patient.

Assessment

Computed tomography scanning was performed every 2 or 3 months to evaluate disease response. Best response during treatment was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[5], and toxicity was evaluated by using the Common Terminology Criteria for Adverse Events (version 4.0[6]). PFS and overall survival (OS) since the start of the chemotherapy were investigated. Cases of conversion therapy were 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 PFS for the first-line regimen and OS. Significant differences were identified by the log-rank test. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

The characteristics of the enrolled patients are summarized in **Table 1**. Median age was 82 years (range, 65-91), and 5 patients were older than 80 years. The participants comprised 3 men and 4 women. The colon and rectum were the primary sites of cancer in 5 and 2 patients, respectively. Six patients were histologically diagnosed with differentiated tumors. On the basis of the Japanese Classification of Colorectal Carcinoma[7], 3 tumors were classified as N0, 3 as N1, and 1 as N2. Furthermore, 3 patients presented with metastasis to the peritoneum and 1 each to a local site, liver, lung, and bone.

Response

The median number of capecitabine + Bmab treatment cycles was 7 (range, 1-17 cycles). No complete or partial response was observed in any patient. The best response during treatment was stable disease, in 5 patients. Thus, the disease control rate was 83.3%, excluding patients who failed in 1 course (**Table 2**). No improvement in PS was observed in any patient during chemotherapy.

Outcomes

Median PFS was 10.0 months (**Fig. 1**). The most common reason for discontinuation of the regimen was disease progression, in 5 patients. The other reasons were a further decrease in PS, in 1 patient, and nonadherence, in 1 patient (**Table 3**).

Three patients underwent second-line therapy: 1 with S-1 and irinotecan + Bmab, 1 with irinotecan + Bmab, and 1 with trifluridine/tipiracil (TAS102). The median OS

for the enrolled patients was 25.8 months (**Fig. 2**).

Dose Intensity

Two of 7 patients did not require dose reduction of capecitabine or Bmab. One patient required a 25% dose reduction for capecitabine after the start of chemotherapy. The other patient ultimately required a 50% reduction of capecitabine and treatment cessation, because of toxicity. Most patients required extension of the rest period. Overall relative dose intensity was 69.5% for capecitabine and 68.4% for Bmab.

Adverse Drug Reactions

The toxicities encountered during the regimen are summarized in **Table 4**. The most common toxicity, of any grade, was hand-foot syndrome, in 3 patients (42.8%). The most common grade 3/4 toxicities were proteinuria and hypertension, in 2 patients (28.6%); 1 patient developed proteinuria and 1 developed hypertension (both grade 3). Because few hematological toxicities were observed, the capecitabine + Bmab regimen was considered well-tolerated. One patient discontinued treatment after the first course because of a further decrease in PS as a result of bowel obstruction. No patient discontinued treatment because of drug toxicity.

Discussion

Although the response rate for the capecitabine + Bmab regimen has been reported to be greater than 30%[8,9], no response was observed in any of the present patients. Furthermore, the present disease control rate was better than that in the AVEX study and similar to that in the MAX study. In the current study, median PFS after first-line treatment was 10.0 months. Feliu et al. reported a median PFS and OS of 10.8 and 18 months, respectively, for 59 mCRC patients aged 70 years or older treated with capecitabine + Bmab as first-line therapy[9]. The OS in the present study was 25.8 months.

The good outcomes for the present PS3 patients may be attributable to the absence of multiple organ metastases, which may have resulted in a lower tumor burden. Additionally, cases considered resectable if patients had good PS might be included. Moreover, basic activities of daily living and nutritional status were maintained in some patients, even when they required prolonged first-line chemotherapy. Toxicity in the current study was significantly lower than in previous studies[1,8,9]. These findings suggest that the capecitabine + Bmab regimen is tolerable for patients with poor PS.

In conclusion, this study found that PFS and OS were favorable in patients with poor PS, despite an inadequate

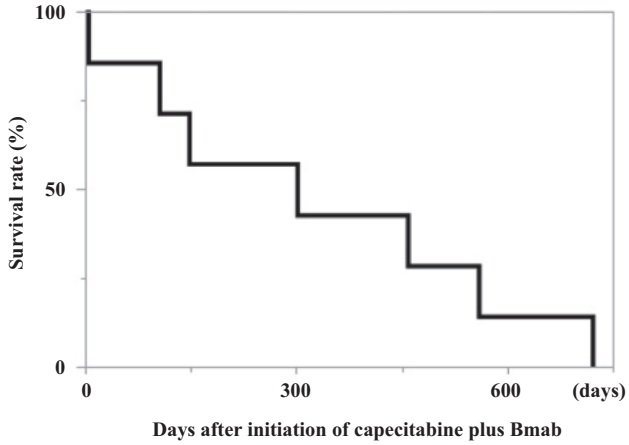

Fig. 1 Kaplan-Meier curve of time to treatment failure.

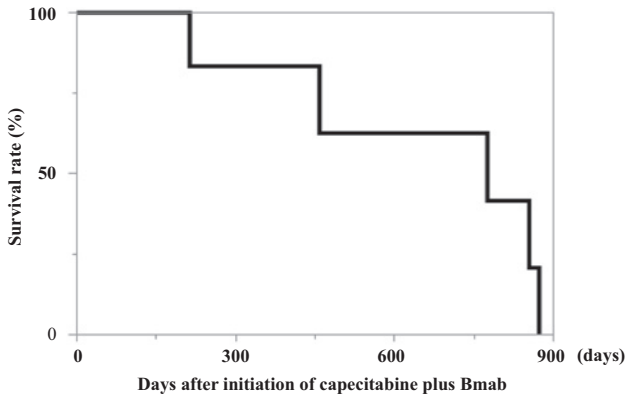

Fig. 2 Kaplan-Meier curve of overall survival.

Table 3 Reasons for discontinuation and second-line treatment

Disease progression		5
Worsened performance status		1
Patient decision		1
Second-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 Events (NCI-CTCAE) version 4.0

		All G	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	1	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

anti-tumor response. Adverse events were considered tolerable because only a few toxicities were noted. These findings suggest that capecitabine + Bmab might yield favorable PFS and OS for vulnerable mCRC patients with poor PS.

Conflict of Interest: The authors declare no conflicts of interest associated with this manuscript.

References

1. Cunningham D, Lang I, Marcuello E, et al. AVEX study investigators. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol [Internet]. 2013 Oct 14 [cited 2020 Jun 26];11:1077−85. Available from: https://doi.org/10.1016/s1470-2045(13)70154-2
2. Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Ann Oncol [Internet]. 2010 [cited 2020 Jun 26];21 (suppl 5):v70−7. Available from: https://doi.org/10.1093/annonc/mdq168
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon cancer Ver. 4. 2020 [cited 2020 Jan 26];. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
4. 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 [Internet]. 2020 Jan 25 [cited 2020 Jun 26];1:1−42. Available from: https://doi.org/10.1007/s10147-019-01485-z
5. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluateon criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer [Internet]. 2009 Jan [cited 2020 Jun 26];45(2):228−47. Available from: https://doi.org/10.1016/j.ejca.2008.10.026
6. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 [Internet]. 2010 Jun 14 [cited 2020 Jun 26]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_4.03.xlsx
7. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal carcinoma. 2nd English Edition. Kanehara Publishing; 2009. p. 1−100. Japanese.
8. Tebbutt NC, Wilson K, Gebski VJ, Cummins MM, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol [Internet]. 2010 Jul 1 [cited 2020 Jun 26];28(19):3191−8. Available from: https://doi.org/10.1200/jco.2009.27.7723
9. Feliu J, Safont MJ, Salud A, et al. Capecitabine and bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer. Br J Cancer [Internet]. 2010 May 11 [cited 2020 Jun 26];102(10):1468−73. Available from: https://dx.doi.org/10.1038%2Fsj.bjc.6605663

(Received, June 30, 2020)
(Accepted, September 11, 2020)
(J-STAGE Advance Publication, September 30, 2020)