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Effects of Type of Antibody to EGFR and Hypomagnesemia on Overall Survival in First-line Treatment of Patients With Unresectable Advanced/Recurrent Colorectal Cancer

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Abstract. *Aim: To clarify the differences in overall survival (OS) depending on the presence or absence of hypomagnesemia and the type of epidermal growth factor receptor antibody as first-line therapy for metastatic colorectal cancer (mCRC). Patients and Methods: We retrospectively compared the OS in 68 patients who received cetuximab or panitumumab for mCRC at Ogaki Municipal Hospital (Ogaki, Japan) between January 2010 and December 2019. Results: The complete and partial response rates in the cetuximab and panitumumab groups were 60.0% and 72.0%, respectively (p=0.470). The OS was significantly longer in the panitumumab group (median=1,007 days, range=208-1,433 days) than in the cetuximab group (median=735 days, range=181-2,391 days; p=0.047). Hypomagnesemia did not contribute to differences in OS in the two groups. Conclusion: Panitumumab may lead to a longer OS than cetuximab as first-line treatment of mCRC. The presence or absence of hypomagnesemia in cetuximab- or panitumumab-treated patients did not affect OS.*

Cetuximab and panitumumab are monoclonal antibodies used as standard treatments for unresectable metastatic colorectal cancer (mCRC) that target the epidermal growth factor receptor (EGFR) (1). EGFR antibodies (cetuximab and panitumumab) are usually first-line therapies used in combination with fluorouracil, leucovorin, and oxaliplatin/fuorouracil, leucovorin, and irinotecan

(FOLFOX/FOLFIRI) therapy in unresectable mCRC with wild-type Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) (2-4). Such therapy results in additional effects on progression-free and overall survival (OS), and the response rate. However, to our knowledge, the OS associated with cetuximab and panitumumab has not been compared.

Hypomagnesemia is an adverse event (AE) of anti-EGFR therapy, and the incidence of severe hypomagnesemia is 4.4-5.4%. Because expression of transient receptor potential melastatin 6 (TRPM6) is regulated by EGF, antibodies targeting EGFR reduce TRPM6 expression and prevent magnesium re-absorption. Thus, hypomagnesemia may indicate the effectiveness of anti-EGFR therapy (5-8) but as far as we are aware, no comparisons exist between the types of EGFR antibodies. In addition, reported correlations between AEs and effectiveness relate only to second and subsequent treatments, and do not compared the relationship in the first treatment.

In this way, the relationships between OS, the type of EGFR antibody and hypomagnesemia in mCRC have not yet been clarified. There is a need to identify patients who can benefit from anti-EGFR treatment; moreover, clarifying the relationship between the type of EGFR antibody and OS can strengthen clinical decision-making and patient outcomes.

Panitumumab has a stronger affinity for EGFR than cetuximab (9), and the risk of developing hypomagnesemia is significantly higher with use of panitumumab (10). The purpose of this study was to clarify the relationship between the type of EGFR antibody (panitumumab and cetuximab), magnesium level, and OS in first-line treatment in patients with mCRC. We hypothesized that panitumumab is associated with a higher incidence of hypomagnesemia than cetuximab, and that its effect on OS would be significant.

Patients and Methods

Patients and evaluations. We retrospectively reviewed 71 patients who received cetuximab or panitumumab for mCRC (stage IV) at Ogaki Municipal Hospital (Ogaki, Japan) between January 2010 and December 2019. However, we excluded three patients who were transferred to another hospital during the treatment or did not receive more than two courses of EGFR antibody therapy. Thus, 68 patients were eligible for this study. Patient characteristics, OS, treatment period, response rate, reason for discontinuation, and AEs (hypomagnesemia) were analyzed using data collected from

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Key Words: Cetuximab, panitumumab, first-line treatment, overall survival, metastatic colorectal cancer, hypomagnesemia.

Table I. *Patient characteristics*.

		Cetuximab (n=37)	Panitumumab (n=31)	*p*-Value
Age, years	Median (range)	64 (37-80)	68 (47-78)	0.910
Gender, n	Male	19	14	0.611
	Female	18	17	
Height, cm	Median (range)	161 (141-175)	162 (145-177)	0.440
Weight, kg	Median (range)	58 (32-82)	52 (41-90)	0.130
Body surface area, m^2	Median (range)	1.61 (1.22-1.98)	1.54 (1.35-1.99)	0.190
Disease status, n	Recurrent	14	5	0.101
	Unresectable	21	20	
Treatment, n	Irinotecan	2	0	0.189
	FOLFIRI	13	4	**0.041**
	FOLFOX	22	27	**<0.001**
Pre-chemotherapy test values, median (range)	Aspartate aminotransferase, IU/l	27 (11-84)	24 (9-147)	0.260
	Alanine aminotransferase, IU/l	24 (7-65)	20 (5-38)	0.181
	Serum creatinine, mg/dl	0.58 (0.33-1.21)	0.73 (0.43-1.69)	0.972
	Total bilirubin, mg/dl	0.50 (0.3-1.4)	0.40 (0.1-0.9)	0.057
	Neutrophil count, n /mm^3	3,110 (1,440-6,140)	3,830 (2,390-8,830)	0.987
	Leukocyte count, n/mm^3	5,170 (2,580-8,100)	6,545 (3,890-9,990)	0.996
	Platelet count, $\times10^4$/mm^3	26.6 (9.7-55.5)	28.3 (13.6-49.0)	0.826
	Serum magnesium, mg/dl	1.9 (1.6-2.6)	2.1 (0.6-2.3)	0.937
Metastatic site, n	Liver	21	24	0.072
	Lung	6	3	0.428
	Lymph node	10	5	0.280
	Peritoneal	9	1	**0.014**
	Bone	1	0	0.356
	Skin	1	0	0.356
	Pleura	1	0	0.356
	Lumbar	1	0	0.356
	Adrenal gland	0	1	0.271
Conversion surgery	Yes	3	10	**0.012**

FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; FOLFIRI: fluorouracil, leucovorin, and irinotecan. Statistically significant *p*-values are shown in bold.

electronic charts and pharmacy service records. The occurrence of hypomagnesemia (<1.5 mg/dl) after starting anti-EGFR treatment were evaluated according to receiving either cetuximab or panitumumab. Patient characteristics were extracted from anonymized patient records. The most severe grades of AEs were evaluated according to the Common Terminology Criteria for AEs, version 4.0 (11). The study's retrospective protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; 20200924-2), and the requirement for informed consent was waived based on the retrospective nature of the study. OS was defined as the interval between the date of initiation of cetuximab or panitumumab therapy and the date of death from any cause. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (12).

Statistical analysis. We evaluated the differences between the two patient groups using either the Mann–Whitney *U*-test or Fisher's exact probability test. The Kaplan–Meier log-rank test was used to compare OS. Significance was defined as $p<0.05$, and all statistical analyses were performed using EZR software (v1.30; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (13).

Results

Patient characteristics. The cetuximab and panitumumab groups comprised 37 and 31 patients, respectively. The patient characteristics are summarized in Table I. The median age of the patients in the cetuximab and panitumumab groups was 64 (range=37-80) and 68 (range=47-78) years, respectively. The cetuximab group had a higher percentage of patients with peritoneal metastases than the panitumumab group ($p=0.014$).

Development of hypomagnesemia according to anti-EGFR treatment. Hypomagnesemia was significantly ($p=0.009$) more frequently observed in patients who received cetuximab (seven out of 37) than in those who received panitumumab (15 out of 31).

Response rate and reasons for discontinuation. The response rate (complete plus partial responses) in the cetuximab and panitumumab groups was 60.0% and 72.0%, respectively, with

Table II. *Comparison of response rate between cetuximab- and panitumumab-treated groups.*

Response	Therapy group		*p*-Value
	Cetuximab (n=37)	Panitumumab (n=31)	
PD	2	0	0.189
SD	12	11	0.791
PR	20	17	0.948
CR	1	1	0.899
Not evaluated	2	2	0.855
Response rate (CR+PR)	21	18	0.470
	60.0%	72.0%	

PD: Progressive disease; PR: partial response; SD: stable disease; CR: complete response.

Table III. *Reasons for discontinuation after first-line treatment.*

Reason	Cetuximab (n=37)	Panitumumab (n=31)	*p*-Value
Progressive disease	26	9	**0.001**
Adverse events	4	3	0.878
Conversion surgery	3	10	**0.012**
Complete response	1	1	0.899
Deterioration of condition	1	2	0.453
Other	1	1	0.899
Ongoing treatment	1	5	0.051

Statistically significant *p*-values are shown in bold.

no significance (p=0.470) (Table II). Rates of progressive disease, stable disease, partial response and complete response did not differ significantly between the two groups.

Table III summarizes the reasons for discontinuation of first-line treatment (cetuximab or panitumumab). Discontinuation was significantly more common for panitumumab (32.3%) than cetuximab (8.1%) in patients undergoing conversion surgery after treatment with anticancer drugs (p=0.012), whilst the converse was true for patients with progressive disease (72.3% *vs*. 29.0%, respectively; p=0.001).

Overall survival and treatment duration according to hypomagnesemia. Figure 1 summarizes the treatment duration according to the presence or absence of hypomagnesemia. In patients using cetuximab, the median treatment duration was 296 (range=168-585) and 259 (range=72-1,001) days, in patients with and without hypomagnesemia, respectively, with no significance (p=0.683). In patients using panitumumab, the duration of treatment in those with hypomagnesemia was significantly longer (p=0.043) at 271 (range=28-658) days than in those without (150 days, range=42-568 days), respectively. Overall, in patients using cetuximab, the median OS was 581 (range=228-868) and 717 (range=181-2,391) days in those with and without hypomagnesemia respectively, with no significance (p=0.101). In those using panitumumab, the corresponding OS was 576 (range=236-1,433) and 528 (range=207-1,251) days, respectively, with no significance (p=0.345).

OS and treatment duration by type of EGFR antibody. Figure 2 shows the Kaplan–Meier survival curves for treatment duration and OS of patients administered cetuximab or panitumumab as first-line treatment. The median duration of cetuximab and panitumumab treatment was 275 (range=72-1001) and 176 (range=28-658) days, respectively (log-rank test, p=0.382; Figure 2A). The OS was significantly longer in the panitumumab group at 1,007 (range=208-1,433) days than that in the cetuximab group of 735 days (range=181-2,391; p=0.047; Figure 2B).

Discussion

In this study, we clarified the differences in OS depending on the type of EGFR antibody as first-line therapy in mCRC and the presence or absence of hypomagnesemia. Although there was no difference in response rate between the panitumumab- and cetuximab-treated with groups, our results indicated that OS was longer practically a third for those treated with panitumumab compared with those treated with cetuximab. The panitumumab group (32.3%) also had a higher proportion of conversion surgery than the cetuximab group (8.1%). Conversely, the development of hypomagnesemia did not affect OS.

Petrellir *et al*. also reported that panitumumab was associated with a significantly increased risk of hypomagnesemia compared with cetuximab (10). The occurrence of grade 3-4 hypomagnesemia was also higher in the panitumumab group [35 (7%) *vs*. 13 (3%)] in the phase III ASPECCT study on mCRC (1). In our study, the incidence of hypomagnesemia was higher in the panitumumab group than in the cetuximab group. It has been reported that the development of hypomagnesemia prolongs treatment with EGFR antibodies (5). However, these were not individual comparisons of cetuximab and panitumumab. In our study, comparisons of the duration of treatment according to hypomagnesemia revealed a difference only in the panitumumab-treated group. Panitumumab has a stronger affinity for the extracellular domain of the EGFR than does cetuximab (9). Our study showed that hypomagnesemia did not affect OS, albeit this was possibly owing to the small sample size.

No reports have directly compared the subsequent OS of patients treated with EGFR antibodies as first-line treatments for mCRC. In chemotherapy-refractory, ASPECCT study findings showed that panitumumab was non-inferior to cetuximab and that these agents provide similar OS benefits in this patient

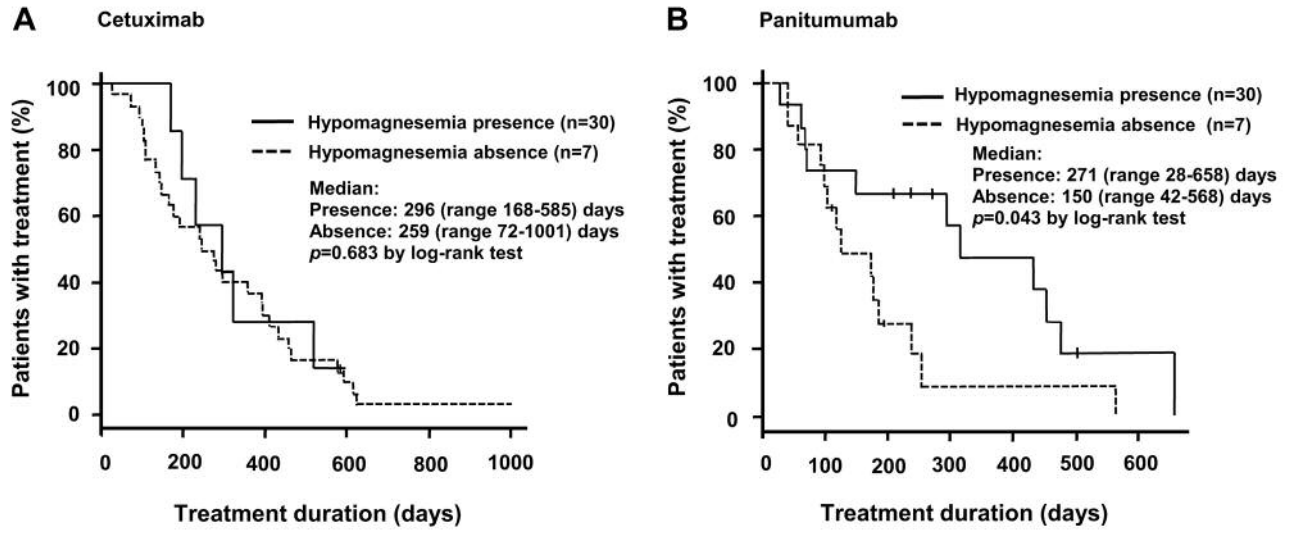

Figure 1. *Kaplan–Meier survival curves of treatment duration according to presence or absence of hypomagnesemia in patients with metastatic colorectal cancer treated with panitumumab or cetuximab.*

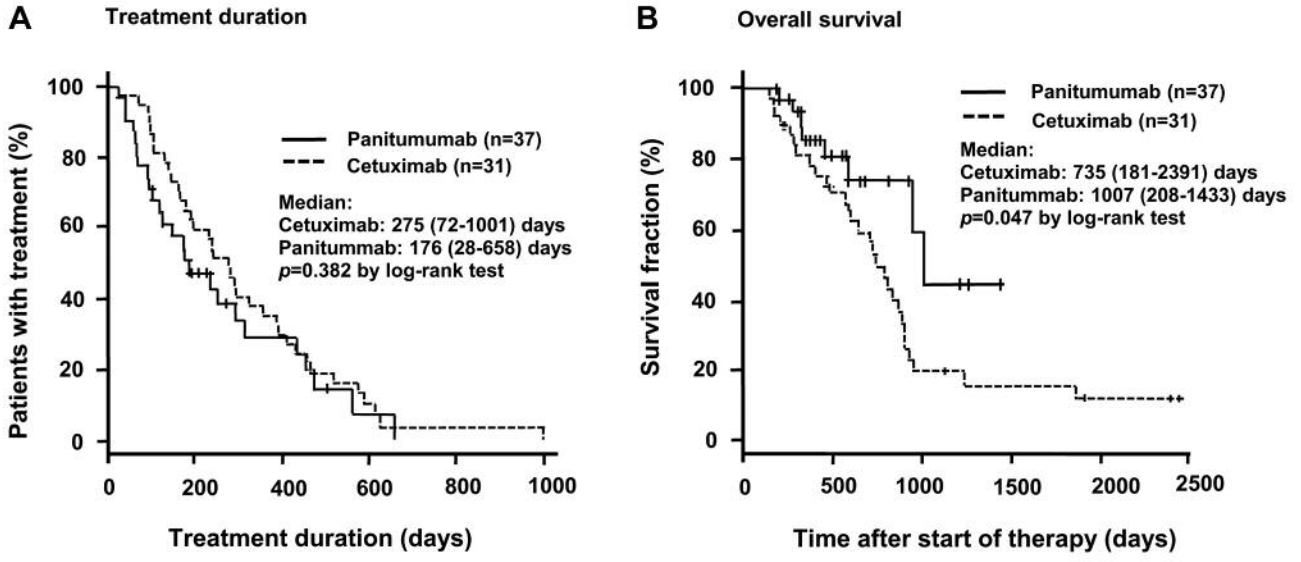

Figure 2. *Kaplan–Meier survival curves of treatment duration and overall survival following first-line therapy of metastatic colorectal cancer with panitumumab or cetuximab.*

population, with median OS of 10.4 months with panitumumab and 10.0 months with cetuximab (1). For *KRAS* wild-type mCRC previously treated with fluoropyrimidine, oxaliplatin and irinotecan, panitumumab with irinotecan was well tolerated, and displayed a similar level of efficacy to that of cetuximab plus irinotecan (14). Using a systematic literature search, Ciliberto *et al*. reported that FOLFOX plus panitumumab has the ability to provide improvements in survival with a good safety profile, particularly in patients with RAS wild-type mCRC on first-line treatment (15). In our study, OS was significantly longer in panitumumab than in cetuximab patients.

In a phase II study comparing treatment regimen with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with modified FOLFOXIRI plus panitumumab administration as a first-line treatment for RAS wild-type mCRC, it was found that the combination treatment benefited

patients eligible for chemotherapy who had a high tumor burden or were aiming for secondary resection of metastases. The group treated with modified FOLFOXIRI plus panitumumab had a significantly higher response (87.3%) and secondary resection rate of metastatic lesions (33.3%). Progression-free survival was similar in both groups but OS tended to be better in the combination group (median=35.7 months) (16). In our study, response rates for the two groups were similar. However, OS was longer for those treated with panitumumab. Panitumumab was more frequently discontinued because of conversion surgery than cetuximab. Conversion surgery transforms advanced inoperable cancer using chemotherapy into a smaller resectable tumor, with excision of the affected area by surgical intervention when the curative intent is evident via imaging. Chemotherapy is the treatment of choice for patients with stage IV cancer. Conversion surgery (curative surgery on patients responding to chemotherapy) may contribute to long-term survival (17-20); therefore, a plausible explanation for the higher OS in the panitumumab-treated group may be attributed to the effects of conversion surgery.

The present study has several limitations. Firstly, the findings are limited due to the lack of standardized prospective tests. Secondly, the primary lesions were not considered separately. A large difference in prognosis is recognized depending on the primary site (right or left) of CRC. Patients with right primary CRC treated with bevacizumab and patients with left primary treated with anti-EGFR had longer survival times (21). Thus, well-designed studies are needed to address these factors and validate our results.

In conclusion, we believe that physicians and pharmacists must collaborate to monitor hypomagnesemia as an AE of treatment; panitumumab may lead to a longer OS than cetuximab in the first-line treatment of mCRC.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

MK contributed to the design of the case report, collection, and provision of data. MK is the principal author of the article, and the guarantor of the article and all the data. EU and TY contributed to the clinical studies design, reviewed the article, and supervised the report and publication process. All Authors approved the final version of the article.

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