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Analysis of the necessity of serum electrolyte monitoring for up to eight weeks after the completion of anti-epidermal growth factor receptor antibody administration

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Electrolyte disturbances are a known side effect of cetuximab (cmab) and panitumumab (pmab) administration and monitoring is recommended during and for at least 8 weeks after pmab administration. However, the recommended duration of electrolyte monitoring is not stated on the cmab package insert in the EU or Japan and no previous studies have investigated the appropriate monitoring period for cmab and pmab. We retrospectively investigated electrolyte levels in 16 cmab-treated patients and 7 pmab-treated patients between 1 June 2009 and 31 December 2014. The mean minimum levels of serum magnesium, potassium, and calcium were analyzed in these patients before administration (baseline) and in period A (during administration), period B (time of the last administration), period C (from the completion of administration to 4 weeks after), and period D (from 4-8 weeks after administration). Hypokalemia persisted until period D in 1 cmab-treated patient. Hypomagnesemia persisted until period D in two pmab-treated patients and hypokalemia persisted until period D in 1 pmab-treated patient. In addition, the serum magnesium levels in periods A, B, and C in the cmab-treated patients were significantly lower than the baseline level ($P < 0.05$). In pmab-treated patients, the serum magnesium levels in periods A, C, and D, and the serum calcium levels in periods A, B, and C were lower than the baseline levels ($P < 0.05$). These findings indicate that it is necessary to monitor electrolyte levels for at least 8 weeks after the completion of administration of cmab or pmab.

1. Introduction

Monoclonal antibodies raised against the epidermal growth factor receptor (EGFR) bind to this receptor with higher affinity than the epidermal growth factor and produce anti-tumor effects by inhibiting signal transduction. At present, two anti-EGFR antibodies are used in clinical practice. Cetuximab (cmab) has been approved for patients with metastatic colorectal cancer (CRC) and head and neck cancer, while panitumumab (pmab) has been approved for CRC.

Electrolyte disturbances are a known side effect of the administration of cmab or pmab. Wang et al. (2006) conducted a meta-analysis of the incidence of electrolyte disturbances in patients receiving anti-EGFR antibodies and reported that 34% showed hypomagnesemia, 14.5% showed hypokalemia, and 16.8% showed hypocalcemia. Therefore, it is very important to monitor serum electrolytes in these patients. The recommended monitoring duration for individuals receiving these two agents differs between countries. Periodic monitoring of serum electrolytes [serum magnesium (s-Mg), serum potassium (s-K), and serum calcium (s-Ca)] is recommended during and for at least 8 weeks after the completion of pmab administration in the USA, the EU, and Japan. This monitoring is specified on the relevant information relating to the injectable pmab formulation: Vectibix® (panitumumab) Injection, Prescribing Information, Amgen Inc., revised 02/2015; Vectibix® (panitumumab) Injection, Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000741/WC500047710.pdf, revised 01/2015); Vectibix® (panitumumab) Injection, Interview Form, Takeda Pharmaceutical Co., Ltd., revised 04/2015. This is considered necessary because 1 patient who developed hypomagnesemia had not recovered by 4 weeks after the completion of Vectibix® administration [Vectibix® (panitumumab) Injection, Interview Form, Takeda Pharmaceutical Co., Ltd., revised 04/2015]. For patients receiving an injectable formulation of cmab (Erbitux®), the USA prescribing information recommends serum electrolyte monitoring for at least 8 weeks after the completion of administration [Erbitux® (cetuximab) Injection, Prescribing Information, Eli Lilly Inc., revised 04/2015], but this is not specified in the EU summary of product characteristics [Erbitux® (cetuximab) injection, Summary of Product Characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf, revised 06/2009]. Although the package insert in Japan recommends serum electrolyte monitoring after the completion of Erbitux® administration, the monitoring period is not specified [Erbitux® (cetuximab) Injection, Insert Package, Merck Serono Co., Ltd., revised 07/2015]. A number of previous reports have described the onset time and incidence of hypomagnesemia in patients receiving pmab or cmab (Whang and Ryder 1990; Maliaka and Ledford 2010; Nakamoto et al. 2011; Fakih et al. 2010), but none of these investigated the appropriate duration of electrolyte monitoring. Patient management and safety could be improved by the identification of the appropriate electrolyte monitoring period for individuals treated with anti-EGFR antibodies.

We conducted a retrospective investigation of serum electrolytes during five different time periods in patients treated with cmab or pmab at Ichinomiya Municipal Hospital: baseline (less than 1 week before the start of cmab and pmab administration); period A (during antibody administration); period B (time of the last

administration); period C (from the completion of administration to 4 weeks after); and period D (from 4-8 weeks after). We also evaluated the influence of combinations of various oral agents (magnesium oxide agents, diuretics, and anti-osteoporotic agents) on electrolyte disturbances.

2. Investigations and results

2.1. Patient characteristics

Of the 85 patients who received cmab or pmab, 62 were excluded from the evaluation because of incomplete monitoring of all 3 electrolytes (s-Mg, s-K, and s-Ca). In the remaining 23 patients, electrolytes had been continuously tracked during the study period. Sixteen of these patients had received cmab and 7 had received pmab. The characteristics of these patients are shown in Table 1.

2.2. Electrolyte disorders in each patient

Patient electrolyte disorder levels during the 5 study periods are shown in Table 2. For cmab, hypomagnesemia and hypokalemia of grade ≥ 1 were observed in 7 patients (44%) and 4 patients (25%), respectively, in period C. In addition, hypokalemia persisted until period D in one patient (Cmab-9; 6%). Hypocalcemia of grade ≥ 1 was not seen in periods C or D. For pmab, hypomagnesemia, hypokalemia, and hypocalcemia of grade ≥ 1 were observed during period C in 3 patients (43%), 3 patients (43%), and 2 patients (29%),

Table 1: Demographic characteristics of the patients

	Cetuximab	Panitumumab
Total number of patients	n = 16	n = 7
Gender; male/female	13/3	7/0
Age; mean ± SD	63.8 ± 14.1	66.4 ± 4.9
Disease; colorectal cancer/head and neck cancer	0/16	7/0
Previous therapy	TPF[a)] 13 No administration history 3	Bmab-XELOX[b)] 3 Bmab-FOLFIRI[c)] 1 Capecitabine 1 No administration history 2
Chemotherapy regimen	Cmab/RT[d)] 16	Pmab-mFOLFOX6[e)] 2 Pmab-FOLFIRI[f)] 4 Panitumumab only 1
Number of treatment times; median (range)	8 (7–10)	8 (3–25)
Days of dosing period; median (range)	50 (42–63)	154 (28–364)
Serum creatinine at the start of treatment (mg/dL); mean ± SD	0.79 ± 0.16	0.81 ± 0.14

SD; standard deviation
[a)] docetaxel, cisplatin, 5-fluorouracil
[b)] bevacizumab, oxaliplatin, capecitabine
[c)] bevacizumab, irinotecan, l-leukovorin, 5-fluorouracil
[d)] cetuximab, radiation
[e)] panitumumab, oxaliplatin, l-leukovorin, 5-fluorouracil
[f)] panitumumab, irinotecan, l-leukovorin, 5-fluorouracil

Table 2: The mean minimum electrolyte levels in each patient in each period

Patient no.	Gender	Age	Days of dosing period	Treatment times	Magnesium oxide agents	Diuretics	antiosteoporotic agents	Serum creatinine (mg/dL)	Serum electrolyte level (disorder grade)					
									Electrolyte	baseline	period A	period B	period C	period
									s-Mg (mg/dL)	0.8(G3)	0.8(G3)	1.2(G1)	1.1(G2)	1.6
Cmab-1	F	72	43	8	-	-	-	0.63	s-K (mmol/L)	3.1(G1)	3.4(G1)	4.1	3.8	4.1
									cs-Ca (mg/dL)	6.3(G3)	8.4(G1)	9.5	9.4	9.4
									s-Mg (mg/dL)	2.1	1.6	1.9	1.4(G1)	2
Cmab-2	F	31	49	9	-	-	-	0.58	s-K (mmol/L)	4.5	3.3(G1)	3.7	3.1(G1)	4.1
									cs-Ca (mg/dL)	8.6(G1)	9.4	10.7	9.3	9.6
									s-Mg (mg/dL)	1.6	1.3(G1)	1.3(G1)	1.4(G1)	1.8
Cmab-3	M	60	50	8	-	-	-	1.01	s-K (mmol/L)	4.4	3.7	4.8	4.7	4.7
									cs-Ca (mg/dL)	9.2	8.9	8.9	9.3	9.5
									s-Mg (mg/dL)	1.9	1.7	1.9	1.8	1.8
Cmab-4	M	77	50	8	+	-	-	0.85	s-K (mmol/L)	4.8	4.2	4.5	4.5	4.7
									cs-Ca (mg/dL)	9.3	9.3	9.8	9.3	9.5
									s-Mg (mg/dL)	2	1.6	1.6	1.8	1.9
Cmab-5	M	72	42	7	-	-	-	0.89	s-K (mmol/L)	4.7	3.7	3.8	5.1	5.1
									cs-Ca (mg/dL)	9.4	9	9.3	9.2	8.9
									s-Mg (mg/dL)	2.1	1.8	1.8	1.6	2
Cmab-6	M	79	49	8	+	+	-	0.83	s-K (mmol/L)	4.3	4.3	5.5	4.7	4.7
									cs-Ca (mg/dL)	9.5	9.4	9.4	9.3	9.7
									s-Mg (mg/dL)	1.9	1.7	1.9	1.7	1.8
Cmab-7	F	52	49	8	-	-	-	0.59	s-K (mmol/L)	3.8	3.6	4.2	4.7	4.8
									cs-Ca (mg/dL)	9.8	9.2	9.2	9.4	9.6

									s-Mg (mg/dL)	1.7	1.6	1.8	1.5	1.6
Cmab-8	M	37	55	9	+	-	-	0.64	s-K (mmol/L)	4.1	2.8(G3)	3.7	3.3	3.8
									cs-Ca (mg/dL)	9.5	9.5	9.8	9.8	9.4
									s-Mg (mg/dL)	2.8	1.9	2	1.3(G1)	1.5
Cmab-9	M	79	51	9	+	-	+	0.76	s-K (mmol/L)	4.1	4.1	3.9	2.9(G3)	3.1(G2)
									cs-Ca (mg/dL)	9.3	9.3	9.7	9.7	8.7
									s-Mg (mg/dL)	1.9	0.9(G2)	0.9(G2)	1.0(G2)	1.7
Cmab-10	M	67	56	7	-	-	-	1.1	s-K (mmol/L)	4.5	4.1	4.6	5.1	4.8
									cs-Ca (mg/dL)	8.9	9.1	9.7	9.5	9.5
									s-Mg (mg/dL)	1.7	1.4(G1)	1.4(G1)	1.2(G1)	1.7
Cmab-11	M	70	62	9	+	-	+	0.7	s-K (mmol/L)	4.4	3.4(G1)	3.4(G1)	3.5(G1)	4.1
									cs-Ca (mg/dL)	9.6	9.3	8.4	9.3	9.1
									s-Mg (mg/dL)	1.9	1.7	1.7	1.9	1.8
Cmab-12	M	57	63	10	-	-	-	0.66	s-K (mmol/L)	4.4	3.6	4.2	4.6	4.1
									cs-Ca (mg/dL)	8.9	8.2(G1)	9.6	8.9	9.1
									s-Mg (mg/dL)	1.8	1.7	1.5	1.3(G1)	1.6
Cmab-13	M	78	78	9	+	-	-	0.64	s-K (mmol/L)	4.1	3.0(G1)	3.8	3.4(G1)	4.4
									cs-Ca (mg/dL)	9.7	9	9.7	9.4	9.3
									s-Mg (mg/dL)	1.7	1.7	1.7	1.8	1.9
Cmab-14	M	72	72	8	-	-	-	0.88	s-K (mmol/L)	4.1	4.2	5.1	4.6	3.8
									cs-Ca (mg/dL)	9.3	9.2	9.4	9.2	9.2
									s-Mg (mg/dL)	2	1.8	1.8	1.7	1.9
Cmab-15	M	63	63	8	-	-	-	0.84	s-K (mmol/L)	4.6	3.8	4.4	3.8	4
									cs-Ca (mg/dL)	8.9	8.9	9.5	9.2	9.2
									s-Mg (mg/dL)	1.7	1.5	1.8	1.7	1.8
Cmab-16	M	54	54	8	-	-	-	0.99	s-K (mmol/L)	4	3.6	4.6	4.6	4.3
									cs-Ca (mg/dL)	9.8	9.1	9.1	10.1	9.8
									s-Mg (mg/dL)	1.9	1.6	1.7	1.8	1.8
Pmab-1	M	62	210	8	-	-	-	0.65	s-K (mmol/L)	3.8	3.4(G1)	4.1	4	3.5(G1)
									cs-Ca (mg/dL)	9.4	8.7	9.3	9.2	9
									s-Mg (mg/dL)	1.6	0.8(G3)	1.0(G2)	0.8(G3)	1.4(G1)
Pmab-2	M	60	227	12	-	+	-	0.94	s-K (mmol/L)	3.6	3.0(G1)	3.6	3.4(G1)	4.5
									cs-Ca (mg/dL)	10.2	8.0(G2)	8.9	8.5(G1)	10.1
									s-Mg (mg/dL)	2.2	1.5	1.5	1.4(G1)	1.4(G1)
Pmab-3	M	65	154	8	+	-	-	0.83	s-K (mmol/L)	4.5	3.8	3.8	3.8	3.8
									cs-Ca (mg/dL)	9.6	8.8	9	9.2	8.9
									s-Mg (mg/dL)	2.2	1.6	1.7	1.7	1.8
Pmab-4	M	66	128	10	+	+	-	0.65	s-K (mmol/L)	4.6	3.8(G1)	4.4	3.4(G1)	4.1
									cs-Ca (mg/dL)	9.5	9.5	9.3	9.1	9.4
									s-Mg (mg/dL)	2.4	1.4(G1)	1.4(G1)	1.2(G1)	1.7
Pmab-5	M	73	76	6	+	-	-	0.97	s-K (mmol/L)	4	2.5(G3)	3.1(G1)	3.1(G1)	2.5(G3)
									cs-Ca (mg/dL)	9.4	8.1(G1)	8.5(G1)	8.3(G1)	9.5
									s-Mg (mg/dL)	1.9	2	1.9	1.9	1.9
Pmab-6	M	65	28	3	-	-	-	0.63	s-K (mmol/L)	4.4	4	4	4.1	4.5
									cs-Ca (mg/dL)	9.4	9.1	9.1	9	9.6
									s-Mg (mg/dL)	2.2	1.7	2.2	1.8	1.9
Pmab-7	M	74	364	25	+	-	-	1.00	s-K (mmol/L)	3.5(G1)	3.1(G1)	3.7	3.8	4
									cs-Ca (mg/dL)	9.5	8.1(G1)	9	8.8	9.2

Cmab-no., the number of a patient who was administered cetuximab; Pmab-no., the number of a patient who was administered panitumumab; +, present; -, absent; s-Mg, serum magnesium; s-K, serum potassium; cs-Ca, corrected serum calcium by serum albumin; baseline, less than 1 week before the start of cetuximab and panitumumab administration; period A, during administration; period B, time of the last administration; period C, from the completio of administration to 4 weeks after; period D, from 4–8 weeks after; (G no.), the grade of the electrolyte disorder, assessed in accordance with the Common Terminology Criteria for Adverse Events v4.0

respectively. In addition, hypomagnesemia persisted until period D in 2 patients (Pmab-2 and Pmab-3; 29%) and hypokalemia persisted until period D in 1 patient (Pmab-5; 14%). In Pmab-1, hypokalemia was not observed in period C, but was present in period D.

2.3. Comparison of electrolyte levels in the study time-periods

The time-courses of the mean minimum electrolyte levels in patients receiving cmab or pmab are shown in the Fig. For patients treated with cmab, s-Mg levels in periods A, B, and C were lower than the baseline level ($P < 0.05$). For patients treated with pmab, s-Mg levels in periods A, C, and D were lower than the baseline level ($P < 0.05$), and the serum albumin-corrected s-Ca (cs-Ca) levels in period A, B, and C were lower than the baseline level ($P < 0.05$).

2.4. Influence of concomitant medications on electrolytes

We determined the numbers of patients receiving concomitant magnesium oxide agents, diuretics, or anti-osteoporotic agents. Six patients receiving cmab and 4 patients receiving pmab had

taken magnesium oxide agents; there was no significant difference between these rates. One patient in the cmab group and 2 patients in the pmab group were taking diuretics (furosemide, torasemide, or spironolactone) and 2 patients receiving pmab had taken an anti-osteoporotic agent (alfacalcidol); however, we could not analyze these rates statistically because the group sizes were small.

3. Discussion

This study identified hypokalemia in 1 patient 4-8 weeks after the completion of cmab administration (period D). This indicated that electrolyte monitoring was necessary for up to 8 weeks after cmab administration, as is currently recommended for pmab. The need for monitoring following pmab administration was also confirmed by the present study, because some of these patients showed hypomagnesemia and/or hypokalemia during period D.

Moreover, the time-course of the mean minimum electrolyte levels indicated that s-Mg levels in periods A-C were lower than the baseline level in the cmab group ($P < 0.05$). S-Mg levels in periods A, C, and D were below baseline ($P < 0.05$), and cs-Ca levels in periods A, B, and C were below baseline ($P < 0.05$). In addition, the period D levels of s-Mg in the cmab group and of s-K and cs-Ca in the pmab group were not significantly different from those recorded during baseline, although they tended to be lower than the baseline levels. These data confirmed that it would be necessary to monitor electrolytes for 8 weeks after the completion of administration of either of these agents.

Although previous studies reported the onset time and incidence rates of hypomagnesemia in patients treated with anti-EGFR antibodies (Whang and Ryder 1990; Maliaka and Ledford 2010; Nakamoto et al. 2011; Fakih et al. 2010), none have monitored all

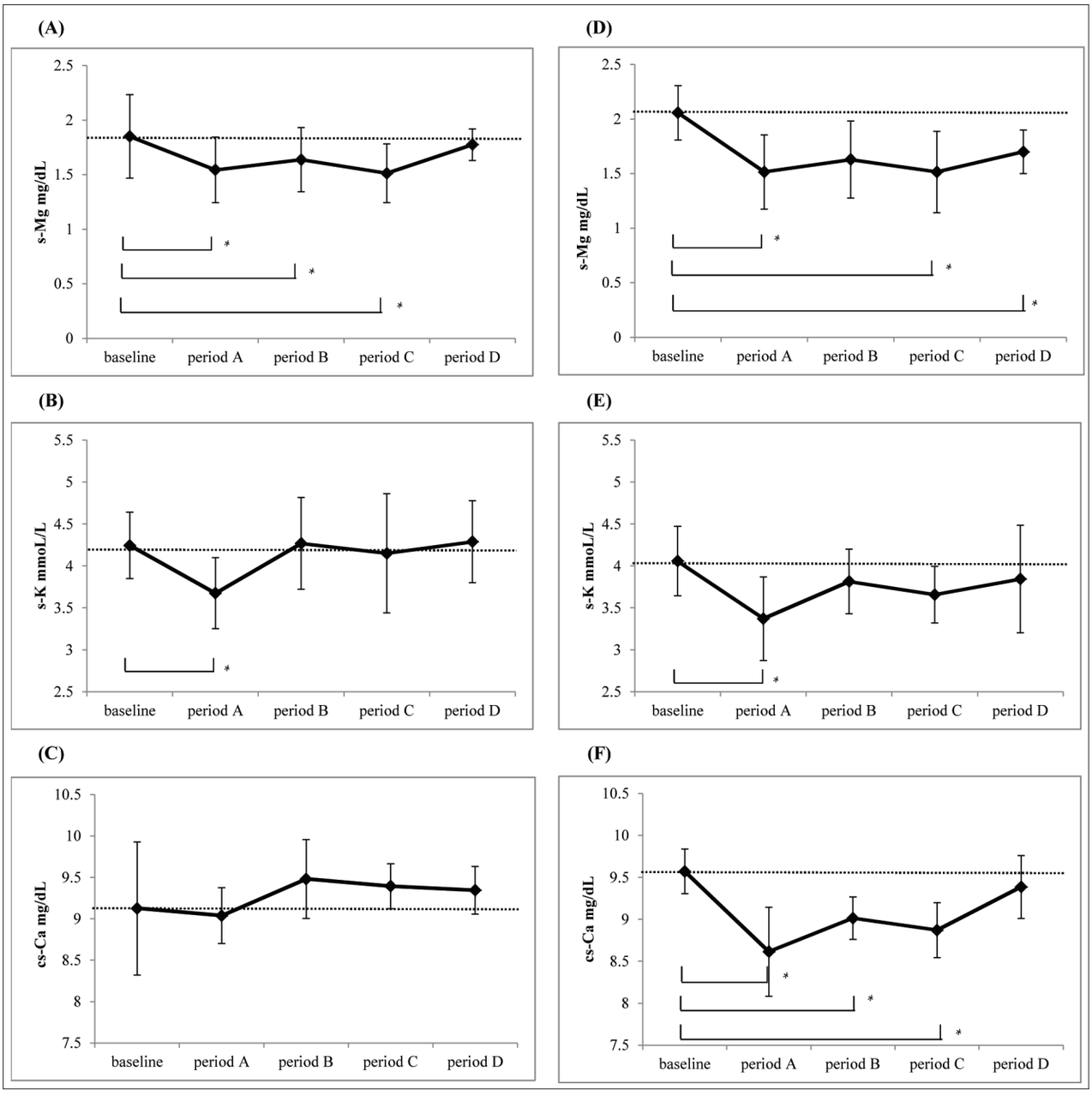

Fig. 1: Time-courses of the mean minimum levels of the indicated electrolytes in the serum of cmab-treated patients (A-C) and pmab-treated patients (D-F). Baseline, less than 1 week before the start of cmab or pmab administration; period A, during administration; period B, time of the last administration; period C, from the completion of administration to 4 weeks after; period D, from 4-8 weeks after; s-Mg, serum magnesium; s-K, serum potassium; cs-Ca, serum calcium, corrected by serum albumin. *P < 0.05, Wilcoxon signed rank test comparison of the indicated mean minimum electrolyte level with that determined prior to antibody administration (baseline).

3 electrolytes (s-Mg, s-K, and s-Ca) continually after the completion of antibody administration. Fakih et al. (2006) reported that 13 of 114 patients treated with cmab for colorectal cancer had grade 3/4 hypomagnesemia, and 3 of these discontinued therapy. The s-Mg levels in 2 of these 3 patients were corrected (to > 1.2 mg/dL) without magnesium supplementation at 1 month from cmab discontinuation, but 1 patient required prolonged and ongoing intravenous supplementation (≥ 5 months) of 4 g, 3 times weekly. A further clinical trial case is mentioned in the pmab interview form, which states that the 'electrolyte disorder did not improve at the time later than 4 weeks after the completion of administration'. However, no further details are provided. In addition, very few reports relating to cmab or pmab have mentioned the duration of hypomagnesemia after the completion of administration (Fakih et al. 2006). Moreover, no reports have assessed the duration of s-K and s-Ca depletion.

The mechanism underlying anti-EGFR antibody-induced hypomagnesemia has not been fully elucidated, although Schrag et al. (2005) reported that the EGFR is strongly expressed in the kidney, particularly in the ascending limb of the loop of Henle, where 70% of filtered magnesium is reabsorbed; EGFR blockade at this site reversibly interfered with magnesium reabsorption. Nakamoto et al. (2011) recommend monitoring from the initiation of treatment because hypomagnesemia may be overlooked due to a lack of noticeable symptoms. The present study confirmed that this is necessary, in addition to continual monitoring after the completion of administration.

It is estimated that more than 50% of patients with clinically significant hypokalemia had a concomitant magnesium deficiency (Haung and Kuo 2007). A decrease in intracellular magnesium, caused by magnesium deficiency, releases the magnesium-mediated inhibition of renal outer medullary potassium channels and increases potassium secretion (Haung and Kuo 2007). Furthermore, magnesium depletion causes impaired synthesis or secretion of parathyroid hormone and thus causes hypocalcemia (Suh et al. 1973). Tejar et al. (2007) reported that hypomagnesemia of grade 2 or higher was associated with hypocalcemia. These findings demonstrate the importance of continuous monitoring for hypokalemia and hypocalcemia, as well as hypomagnesemia, when using anti-EGFR antibodies. The Nakamoto et al. (2011) report on hypomagnesemia during cmab therapy was limited by a lack of data relating to electrolytes other than s-Mg; s-Ca, s-K, and s-P (serum phosphate) were not routinely checked in most cases. Pazo-Oubina et al. (2013) also reported that the magnesium levels in 15-42% of their patients were not analyzed during treatment with anti-EGFR antibodies. Thus, although the number of patients in the present study was small, it provides a valuable report of 3 electrolytes, before and after therapy completion. In order to address this issue in our hospital, we hold inter-disciplinary team conferences periodically and clinical pharmacists report the electrolyte levels in the clinical blood samples from all patients receiving cmab and pmab. In this way, electrolyte testing has become routine for almost all patients receiving cmab and pmab.

In this study, we confirmed that electrolyte disturbances tended to be more delayed following administration of pmab, as compared with cmab. This may have been because all of the patients receiving cmab were also treated with radiation, whereas all those receiving pmab (with the exception of 1 patient) were receiving chemotherapy. Ishiguro et al. (2012) reported that 217 patients receiving cmab developed hypomagnesemia; 187 of these were treated with a combination of chemotherapies and 30 were not. This indicated that electrolyte disturbances occurred more frequently in patients receiving combination therapy. In addition, a meta-analysis by Wang et al. (2015) showed that hypomagnesemia and hypokalemia occurred more frequently in patients treated with pmab, as compared to those receiving cmab.

In this study, only 1 of the patients who had ≥ grade 2 electrolyte disturbances was not treated by supplementation using electrolyte drugs. Therefore, in the future, it is necessary for pharmacists to continue to propose the appropriate prescriptions and actively offer information about supplementation.

Consistent with previous reports (Nakamoto et al. 2011; Tejpar et al. 2007), the present analysis of the influence of concomitant agents (magnesium oxide agents, diuretics, or anti-osteoporotic agents) on electrolytes detected no relationship between magnesium oxide agents and hypomagnesemia. There is a possibility that no difference was observed because of the small number of patients analyzed, although this finding could also reflect the poor absorption of magnesium oxide from the intestinal tract. We could not analyze the effects of concomitant diuretics and anti-osteoporotic agents because of the small number of patients involved. However, a previous study reported no relationship between diuretics and hypomagnesemia (Tejpar et al. 2007). In the 2 patients who had taken an anti-osteoporotic agent (alfacalcidol) in the present study, we observed hypomagnesemia but not hypocalcemia. This indicated that it is possible to prevent hypomagnesemia-associated hypocalcemia. This issue warrants further investigation in the future.

Recently, Price et al. (2015 ASCO GI, #705) reported the outcomes of the ASPECCT trial for CRC. In this study, patients treated with cmab or pmab who developed any grade of hypomagnesemia showed higher objective response rates, progression-free survival, and overall survival, as compared with those who did not develop hypomagnesemia. This indicated that it is important to continue treatment, along with the appropriate management of hypomagnesemia; pharmacists should therefore enhance monitoring and management of hypomagnesemia.

This study had the limitation of being a retrospective study. Although we evaluated 85 patients, only 23 had received the 3 necessary electrolyte tests at baseline and for up to 8 weeks after the completion of antibody administration. The types of cancer diagnoses in patients receiving cmab and those receiving pmab were different. In addition, we analyzed the minimum levels of electrolytes within each time-period, rather than measuring these at a fixed time-point. However, it was not possible to use a consistent measurement point because the number of administrations, and the administration period, differed between the patients. In the future, it would be useful to conduct an investigation of serum electrolytes beyond 8 weeks after the completion of administration.

In conclusion, our results suggested that electrolyte levels should be monitored in patients treated with cmab and also pmab for up to 8 weeks after the completion of drug administration.

4. Experimental

4.1. Subjects

The study subjects were selected from 85 patients who received cmab or pmab for CRC or head and neck cancer at Ichinomiya Municipal Hospital between 1 June 2009 and 31 December 2014.

4.2. Data collection

We collected data relating to s-Mg, s-K, and s-Ca from electronic medical records for each of the study time-periods (baseline, period A, period B, period C, and period D). We calculated the cs-Ca using the serum albumin level. In addition, we recorded the presence or absence of concomitant medication (magnesium oxide agents, diuretics, and anti-osteoporosis agents).

4.3. Data evaluation

As the primary endpoints, we examined: (1) electrolyte disorders in each patient; (2) time-course of the mean minimum electrolyte levels in each time-period. As a secondary endpoint, we evaluated the influence of magnesium oxide agents, diuretics, and anti-osteoporotic agents on electrolyte disorders. The electrolyte disorder grades were assessed in accordance with the Japan Clinical Oncology Group, Japanese version of the Common Terminology Criteria for Adverse Events v4.0 (http://www.jcog.jp/doctor/tool/ctcaev4.html).

4.4. Statistical analysis

The Wilcoxon signed rank test was used for comparison of the mean minimum electrolyte levels between baseline and each time-period (A, B, C, or D). Fisher's exact test was used for comparison of the electrolyte disorders in the presence/absence of magnesium oxide agents, diuretics, or anti-osteoporotic agents. All analyses were conducted using EZR software (version 1.0, CHUGAI-IGAKUSYA, Japan). All P values of less than 0.05 were considered statistically significant.

4.5. Ethical considerations

The implementation and publication of the results of this study were conducted in accordance with the appropriate handling of personal information and with the approval of the clinical research review committee at Ichinomiya Municipal Hospital.

Conflict of interest: There are no conflicts of interest to declare.

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