Refractory hypokalemia caused by cetuximab with advanced colorectal cancer patients: the case series and literature review

Yun-Wang Chen[a,b], Min Yang[a], Ming-Xing Wang[b,c], Jia-Hong Jiang[b], Ding-Yi Jiang[a,b], Zhe-Ling Chen[b] and Liu Yang[a,b]

Cetuximab is the first-line treatment for advanced metastatic colon cancer. But cetuximab can cause electrolyte disturbances, including hypomagnesemia and hypokalemia. Among them, hypokalemia is often caused by hypomagnesemia, not directly caused by cetuximab. This article reports two cases of refractory hypokalemia caused by cetuximab without hypomagnesemia. The two patients had no abnormalities in serum potassium before cetuximab treatment. The occurrence of hypokalemia was clearly correlated with the cetuximab, and they were significantly improved after stopping or reducing the dose. At the same time, the appearance of hypokalemia is significantly related to the efficacy of cetuximab. They have received 37 and 35 cycles of cetuximab-related therapy, with condition stable periods of 12.8 and 15.1 months, respectively. Obviously, our report refutes the above view. In our opinion, hypokalemia, a side effect of cetuximab, may be directly caused by it, rather than secondary to hypomagnesemia. Similar to hypomagnesemia, the appearance of hypokalemia often indicates a better curative effect of cetuximab. *Anti-Cancer Drugs* 33: e789–e794 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Anti-Cancer Drugs 2022, **33**:e789–e794

Keywords: adverse effects, case report, cetuximab, colorectal cancer, hypokalemia, hypomagnesemia

[a]The Qingdao University Medical College, Qingdao, Shandong, [b]Cancer Center, Department of Medical Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, Zhejiang and [c]Graduate School of Clinical Medicine, Bengbu Medical College, Bengbu, Anhui Province, China

Correspondence to Zhe-Ling Chen, PhD, Cancer Center, Department of Medical Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, Zhejiang 310014, P. R. China
Tel: +18329114675; e-mail: chenzheling@hmc.edu.cn

Received 19 July 2021 **Revised form accepted** 19 July 2021

Introduction

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor. Cetuximab can inhibit the downstream signaling pathway of EGFR, reduce the invasion and spread of tumor cells to normal tissues, and can also achieve anti-tumor effects by inhibiting the formation of new blood vessels in tumor tissue [1,2]. Compared with FOLFIRI (irinotecan, leucovorin plus fluorouracil) or FOLFOX (oxaliplatin, leucovorin plus fluorouracil) chemotherapy alone, the addition of cetuximab has a better curative effect and can improve patients' response rate, progression-free survival (PFS), and overall survival (OS) [3–5]. It can be seen that cetuximab is the first-line choice for advanced RAS wild-type colorectal cancer because it has better efficacy, fewer adverse reactions, and higher tolerance [5,6]. However, cetuximab may also cause some adverse events such as neutropenia, diarrhea, rash, and other common adverse reactions [7]. At the same time, it can also cause hypokalemia, hypomagnesemia, hypocalcemia, and other electrolyte disturbance through direct renal toxicity and affecting related ion channels [8,9]. Cetuximab has the highest incidence of hypomagnesemia in patients with colorectal cancer. Some studies have reported that the incidence of hypomagnesemia is about 17%, another meta-analysis reported the incidence of grade 3/4 hypomagnesemia in the cancer group is about 2.9%, and the mechanism of hypomagnesemia has not been studied clearly [10,11]. In terms of hypokalemia, a meta-analysis reported that the incidence of all-grade hypokalemia caused by cetuximab was about 8%, of which the incidence of high-grade hypokalemia was about 6.2%, the mechanism of which remains unclear [12]. Some researchers reported that hypomagnesemia will lead to a decrease of Na^+–K^+–ATPase activity on the cell surface, which leads to a decrease of K^+ influx and excessive loss from the kidney, which leads to a decrease of serum potassium, rather than the direct effect of cetuximab, meanwhile there are pieces of evidence that potassium and magnesium supplementation can alleviate hypokalemia levels [8,13,14]. The study reported on two patients with advanced metastatic colorectal cancer who were treated with cetuximab and caused refractory and isolated hypokalemia without hypomagnesemia. The occurrence of hypokalemia in two patients was clearly related to cetuximab and was significantly improved after stopping or reducing the dose.

0959-4973 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

DOI: 10.1097/CAD.0000000000001212

Case report

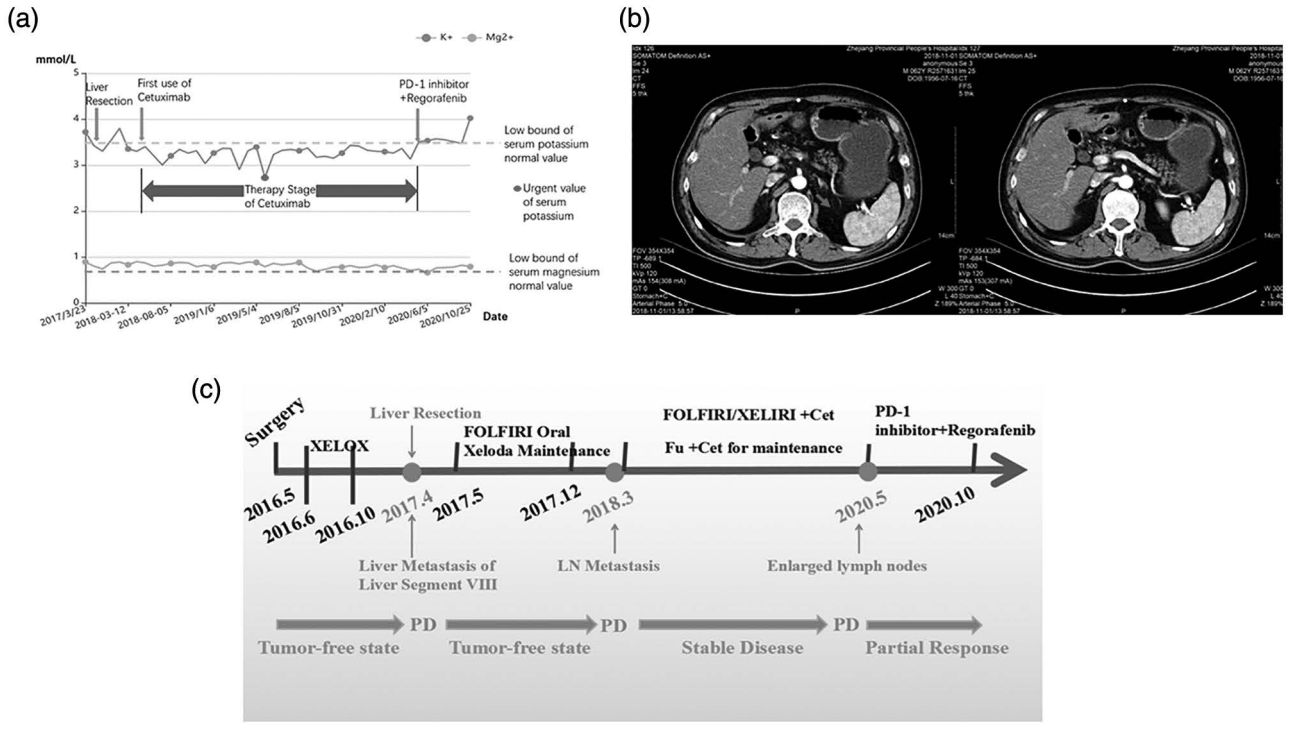
Case 1

A 64-year-old patient underwent 'radical resection of transverse colon cancer' on 10 May 2016. The pathological results of the patient showed that it was adenocarcinoma of the right colon (ulcerative type, medium low differentiation). The immunohistochemical results are as follows: PMS2(+), MSH2(+), MSH6(+), MLH1(+), EGFR(+), pMMR. The genetic testing suggests RAS wild type. He received six cycles of adjuvant chemotherapy with XELOX (Xeloda plus oxaliplatin). In April 2017, the patient had liver recurrence and metastasis. After undergoing surgical resection of liver metastases, the patient received the FOLFIRI chemotherapy regimen for eight cycles and oral Xeloda to maintain chemotherapy for two cycles. In March 2018, the patient's liver MRI showed that the liver recurred again and the disease was progressing. Since 1 March 2018, the patient has received chemotherapy combined with cetuximab. Due to changes in the condition until 16 May 2020, cetuximab combined with FOLFIRI, XEIRI (Xeloda plus irinotecan), and fluorouracil for 37 cycles, with condition stable periods of 12.8 months. Since the administration of cetuximab on 1 March 2018, the patient has presented with refractory hypokalemia: 3.224 ± 0.182 mmol/L, with the lowest value of 2.73 mmol/L and the highest value 3.40 mmol/L. After cetuximab was stopped, serum potassium levels gradually returned to normal (Fig. 1a). Considering that patient 1's condition worsened due to cetuximab resistance, the patient stopped cetuximab and switched to PD-1 inhibitor (sintilimab) for immunotherapy on 16 May 2020. After stopping cetuximab, the hypokalemia of patient 1 improved. In order to explore the mechanism of hypokalemia, we have performed computed tomography (CT) examination of the adrenal glands, and there was no obvious abnormality (Fig. 1b). The treatment timeline of patient 1 are as follows (Fig. 1c).

Case 2

A 42-year-old patient underwent 'radical resection of sigmoid colon cancer and microwave ablation of liver metastases' on 5 July 2019 after 12 cycles of cetuximab combined with mFOLFOX6 chemotherapy for conversion treatment. The patient underwent 12 cycles of conversion therapy before surgery, the specific plan was cetuximab combined with chemotherapy. Postoperative pathology indicated moderately differentiated adenocarcinomas of the sigmoid colon and immunohistochemistry indicated that MLH1(+), PMS2(+), MSH2(+), MSH6(+), pMMR, MSS. For patient 2, cetuximab was combined with chemotherapy since the operation. According to the disease condition of patient 2, the dose of cetuximab was reduced from 1.1 to 0.8 g on 16 September

Fig. 1



The clinical data, changes in blood potassium, and treatment history of patient 1. (a) Changes of serum potassium and serum magnesium of patient 1. (b) Patient 1 adrenal glands have no obvious abnormalities as indicated by the red arrows. (c) Treatment timeline of patient 1. Cet, cetuximab; XELOX, Xeloda plus oxaliplatin; FOLFIRI, irinotecan, leucovorin plus fluorouracil; XELIRI, irinotecan plus Xeloda; PD, progressive disease.

2020. On 23 November 2020, the patient stopped cetuximab and switched to bevacizumab. After reducing the dose and stopping cetuximab, the hypokalemia of patient 2 improved, too. He received 35 cycles of cetuximab-related therapy, with a condition stable period of 15.1 months. Since the first use of cetuximab after radical operation, the patient has presented with refractory hypokalemia: 3.146 ± 0.220 mmol/L, with the lowest value 2.64 mmol/L and the highest value 3.78 mmol/L (Fig. 2a). The patient's 24-h urine biochemical test showed no obvious increase in potassium excretion. We also consider whether the patient has adrenal gland disease that causes hypokalemia. CT plain scan (Fig. 2b) showed a slight thickening of the adrenal glands but no obvious space-occupying lesions. The mineralocorticoid test for patient 2 is no abnormality (Fig. 2c). Treatment timelines of patient 1 are as follows (Fig. 2d).

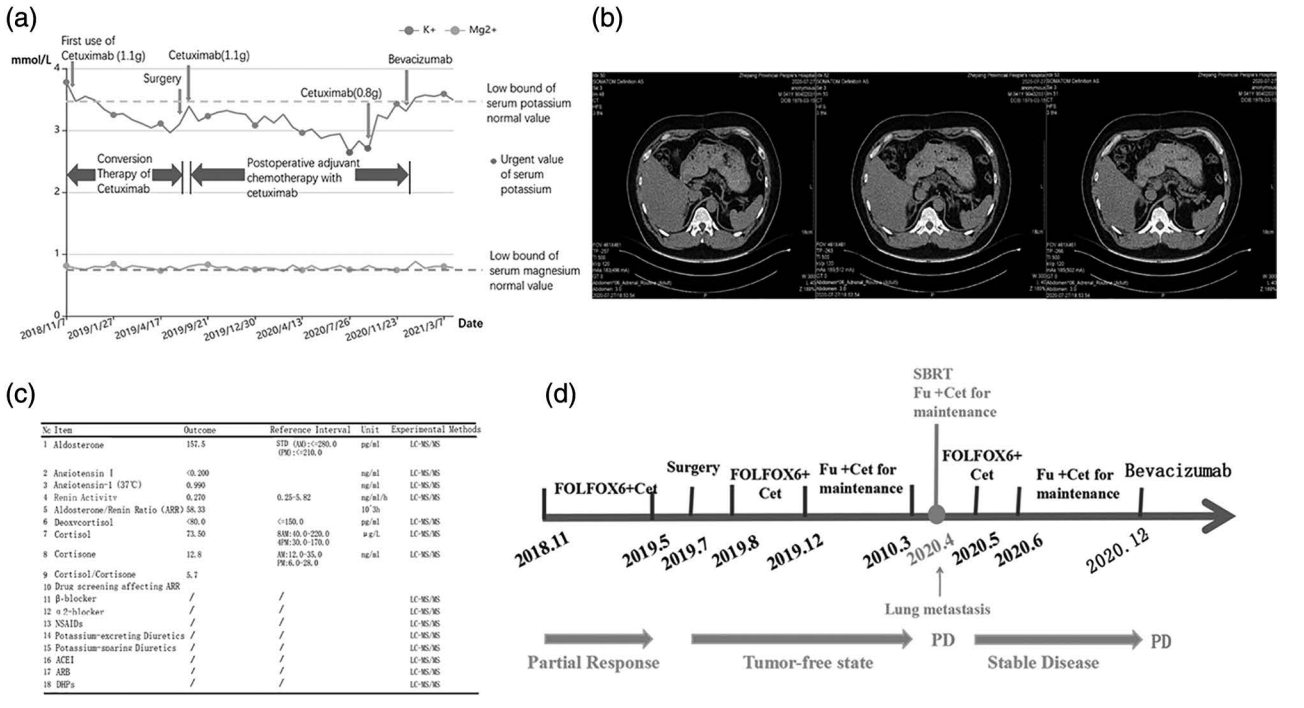
Management and outcome

Active potassium and magnesium supplementation during hospitalization and frequent monitoring of blood potassium levels. Considering that patient 1's condition worsened due to cetuximab resistance, the patient stopped cetuximab and switched to PD-1 inhibitor (sintilimab) for immunotherapy on 16 May 2020. According to the disease condition of patient 2, the dose of cetuximab was reduced from 1.1 to 0.8 g on 16 September 2020. On 23 November 2020, the patient stopped cetuximab and switched to bevacizumab. Two patients are still alive today. After stopping cetuximab, the hypokalemia of patient 1 improved. After reducing the dose and stopping cetuximab, the hypokalemia of patient 2 improved, too. They received 37 and 35 cycles of cetuximab-related therapy, with condition stable periods of 12.8 and 15.1 months, respectively.

Discussion

Cetuximab, an anti-EGFR antibody, combined with chemotherapy has been written into several guidelines as the first-line standard treatment regimen for colorectal cancer [6,15]. However, adverse effects should be taken into account when receiving the efficacy from cetuximab. In this study, the more prominent adverse effect of the two patients was refractory hypokalemia without hypomagnesemia. The influence of cetuximab on electrolytes may be manifested as severe hypomagnesemia, hypokalemia, hypocalcemia, etc., among which hypomagnesemia is the most common, and relevant studies have also been frequently reported [8,16]. Hypomagnesemia caused by cetuximab has not been thoroughly studied, and it may be related to transient receptor potential melastatin 6 and 7 (TRPM6/7) channels

Fig. 2



№	Item	Outcome	Reference Interval	Unit	Experimental Methods
1	Aldosterone	157.5	STD (AM):<260.0 (PM):<210.0	pg/ml	LC-MS/MS
2	Angiotensin I	<0.200		ng/ml	LC-MS/MS
3	Angiotensin-1 (37℃)	0.990		ng/ml	LC-MS/MS
4	Renin Activity	0.220	0.25-5.82	ng/ml/h	LC-MS/MS
5	Aldosterone/Renin Ratio (ARR)	58.33		10^3h	
6	Deoxycortisol	<80.0	<=150.0	pg/ml	LC-MS/MS
7	Cortisol	73.50	AM:40.0-220.0 4PM:30.0-170.0	μg/L	LC-MS/MS
8	Cortisone	12.8	AM:12.0-35.0 PM:6.0-28.0	ng/ml	LC-MS/MS
9	Cortisol/Cortisone	5.7			
10	Drug screening affecting ARR				
11	β-blocker	/	/		LC-MS/MS
12	α2-blocker	/	/		LC-MS/MS
13	NSAIDs	/	/		LC-MS/MS
14	Potassium-excreting Diuretics	/	/		LC-MS/MS
15	Potassium-soaring Diuretics	/	/		LC-MS/MS
16	ACEI	/	/		LC-MS/MS
17	ARB	/	/		LC-MS/MS
18	DRPs	/	/		LC-MS/MS

The clinical data, changes in blood potassium, and treatment history of patient 2. (a) Changes of serum potassium and serum magnesium of patient 2. (b) Patient 2 adrenal glands slightly enlarged on CT plain scan as indicated by the red arrows. (c) Patient 2 mineralocorticoid. (d) Treatment timeline of patient 2. mFOLFOX6, oxaliplatin, leucovorin plus fluorouracil; PD, progressive disease; SBRT, stereotactic body radiation therapy.

[17]. The presence of TRPM6/7 is the biological basis necessary for Mg^{2+} reabsorption, the TRPM6 channel mainly exists in the distal tubules that mediate Mg^{2+} reabsorption, and the TRPM7 channel is expressed on the cell surface of each kidney tissue [18]. EGF is a magnesium affinity hormone that can regulate the activity of TRPM6. Cetuximab, an EGFR blocker, can block TRPM6/7 channel transport, reduce Mg^{2+} reabsorption and increase excretion, leading to hypomagnesemia [18–21].

However, there are few reports of hypokalemia directly caused by cetuximab, and there are still no relevant reports on its mechanism. In a mate-analysis of phase III prospective clinical trials of cetuximab for advanced malignant tumors, it was reported that the incidence of all-grade hypokalemia was about 8%, of which high-grade hypokalemia was about 6.2% [12]. Generally speaking, it is believed that hypokalemia is usually secondary to hypomagnesemia. When serum magnesium is lower than the normal level (0.75–1.25 mmol/L), the influx of potassium ions of the renal outer-medullary K^+ channel (ROM-K) weakens, and K^+ are excreted from the body, leading to hypokalemia [22].

We reported two patients with refractory hypokalemia who were not associated with hypomagnesemia and were given magnesium supplements based on trials, but the hypokalemia was not corrected. This may indicate that the hypokalemia of two patients was related to other factors without hypomagnesemia. First, we clinically verify the independent correlation between cetuximab and hypokalemia reported in this report. According to Naranjo Algorithm Assessment, our total score was seven points, indicating that hypokalemia is likely to be associated with cetuximab (Fig. 3) [23]. Both of them were patients with advanced colorectal cancer who had received long-term cetuximab treatment (37 cycles vs. 35 cycles), and both showed refractory hypokalemia. Serum potassium levels increased steadily after reducing the dose or withdrawal of cetuximab. Both patients were well fed and had no history of insulin treatment. From the discovery of hypokalemia, they have been instructed to eat foods with high potassium content, oral potassium tablets and supplement solution, magnesium supplementation. In order to rule out primary aldosteronism, abdominal CT examinations were performed on two patients. Patient 1 had no obvious abnormalities in the CT of the adrenal glands (Fig. 1b) and patient 2 had a slight enlargement of the adrenal glands (Fig. 2b). CT scans of the adrenal glands of the two patients showed no obvious space-occupying disease. So, we continue to improve the mineralocorticoid test for patient 2, and there is no abnormality (Fig. 2c), which can rule out hyperaldosteronism. In addition, we conducted a detailed investigation on patient 2 and found no other diseases that caused primary hypokalemia. By excluding diagnostic and experimental discontinuation or reducing the dose of cetuximab, we believe that refractory hypokalemia is caused by cetuximab. In addition, hypokalemia is usually secondary to hypomagnesemia. When the magnesium content in the body is lower

Fig. 3

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	*No*	*Do not know*	*Score*
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	+1
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total score	7

Naranjo Algorithm Assessment. According to the results of the total score, it was divided into four grades: 'positive', 'likely', 'possible', and 'suspicious', which were used to describe the degree of causality of adverse reactions. Positive ≥ 9 points; likely 5–8 points; possible 1–4 points; suspicious ≤ 0 points.

than the normal level (0.75–1.25 mmol/L), ROM-K can weaken the influx of potassium ions, increase the excretion of potassium ions from the urine, and lead to hypokalemia [24]. However, the two patients we reported had refractory hypokalemia without hypomagnesemia: patient 1 mean blood magnesium: 0.844 ± 0.037 mmol/L, lowest value 0.78 mmol/L, highest value 0.90 mmol/L; patient 2 mean blood magnesium: 0.777 ± 0.032 mmol/L, lowest value 0.72 mmol/L, highest value 0.84 mmol/L. Meanwhile, trial magnesium supplementation was performed, but hypokalemia was not corrected. This may indicate that hypokalemia among them may be related to the direct nephrotoxicity induced by cetuximab, but the specific mechanism is not clear and further basic mechanism research is needed.

Interestingly, when we collected the survival data of two patients, we found that both patients showed a good response to cetuximab. In a meta-analysis of cetuximab, patients with hypomagnesemia caused by cetuximab showed better PFS (HR: 0.64; 95% CI, 0.47–0.88), OS (HR: 0.72; 95% CI, 0.53–0.92), ORR (RR: 1.81; 95% CI, 1.30–2.52), it is clear that hypomagnesemia is associated with the benefits of PFS [25]. We suspect that hypokalemia is similar to hypomagnesemia, and its degree is positively related to the efficacy of cetuximab. Among them, patient 1 has received 37 cycles of cetuximab-related treatment and was in a stable state for 12.8 months. Patient 2 has received 35 cycles of cetuximab, of which 15.1 months were stable, and is now receiving reduced maintenance cetuximab based on his condition. Compared with the TAILOR trial, these two patients showed better efficacy [26]. We hypothesized that the occurrence of hypokalemia may be an independent predictor of the prognosis of cetuximab, but we have not found relevant reports and studies in the literature, so this hypothesis requires further laboratory evidence.

In the clinic, blood electrolyte content should be closely monitored when cetuximab is used, and potassium should be timely supplemented through gastrointestinal and venous channels when serum potassium decreases. K^+ is an essential metal cation in cells and the material basis for maintaining resting potential. When serum potassium is lower than normal, hypokalemia increases cardiac excitability, reduces conductivity, and increases the autorhythmicity of abnormal exciting points, leading to arrhythmias. It is worth noting that most of the K^+ in the body is present in the intracellular fluid. When the serum potassium starts to decrease, the intracellular K^+ will be removed compensatively to keep the serum potassium stable. When serum potassium reaches a measurable hypokalemia level, it means that there is a lack of potassium in the cells, so it is necessary to supplement potassium in the systemic circulation and intracellular fluid. However, since it is difficult to determine the potassium concentration in the intracellular fluid, the total amount of potassium added is mainly based on the experience of clinicians. So, it is also important to monitor potassium concentration in time during potassium supplementation.

Acknowledgements

The study received informed written consent from all participants. These case studies were based on the principles outlined in the Declaration of Helsinki. The protocol was approved by the ethics committee of the Zhejiang Provincial People's Hospital (2020QT372). Informed written consent was obtained from the patients for publication of this report and any accompanying images.

Conflicts of interest

There are no conflicts of interest.

References

1 Roskoski R Jr. Small molecule inhibitors targeting the EGFR/ErbB family of protein-tyrosine kinases in human cancers. *Pharmacol Res* 2019; **139**:395–411.
2 Miyamoto Y, Suyama K, Baba H. Recent advances in targeting the EGFR signaling pathway for the treatment of metastatic colorectal cancer. *Int J Mol Sci* 2017; **18**:E752.
3 Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, *et al*. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 2015; **33**:692–700.
4 Yamaguchi K, Ando M, Ooki A, Beier F, Guenther S, von Hohnhorst P, Van Cutsem E. Quality of life analysis in patients with RAS wild-type metastatic colorectal cancer treated with first-line cetuximab plus chemotherapy. *Clin Colorectal Cancer* 2017; **16**:e29–e37.
5 Chunlong H, Xiaoyuan G, Xianshang Z, Baomin C, Weiguang Y, Meiji C. Cetuximab versus bevacizumab following prior FOLFOXIRI and bevacizumab in postmenopausal women with advanced KRAS and BRAF wild-type colorectal cancer: a retrospective study. *BMC Cancer* 2021; **21**:30.
6 Colorectal cancer working group C. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for colorectal cancer 2018 (English version). *Chin J Cancer Res* 2019; **31**:117–134.
7 Chen J, Wang J, Ni T, He H, Zheng Q. Meta-analysis on the risk of fatal adverse events by bevacizumab, cetuximab, and panitumumab in 31 randomized trials including 25,000 patients with colorectal carcinoma. *Medicine* 2020; **99**:e19908.
8 Verzicco I, Regolisti G, Quaini F, Bocchi P, Brusasco I, Ferrari M, *et al*. Electrolyte disorders induced by antineoplastic drugs. *Front Oncol* 2020; **10**:779.
9 Jhaveri KD, Wanchoo R, Sakhiya V, Ross DW, Fishbane S. Adverse renal effects of novel molecular oncologic targeted therapies: a narrative review. *Kidney Int Rep* 2017; **2**:108–123.
10 Chen P, Wang L, Li H, Liu B, Zou Z. Incidence and risk of hypomagnesemia in advanced cancer patients treated with cetuximab: a meta-analysis. *Oncol Lett* 2013; **5**:1915–1920.
11 Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Barni S. Risk of anti-EGFR monoclonal antibody-related hypomagnesemia: systematic review and pooled analysis of randomized studies. *Expert Opin Drug Saf* 2012; **11**(suppl 1):S9–19.
12 Cao Y, Liu L, Liao C, Tan A, Gao F. Meta-analysis of incidence and risk of hypokalemia with cetuximab-based therapy for advanced cancer. *Cancer Chemother Pharmacol* 2010; **66**:37–42.
13 Margaux VW, Joanne F, Hamza S, Mario O, Dil S, Hassan I, *et al*. Nephrotoxicity of anti-angiogenic therapies. *Diagnostics (Basel, Switzerland)* 2021; **11**:640.
14 Weir MR, Espaillat R. Clinical perspectives on the rationale for potassium supplementation. *Postgrad Med* 2015; **127**:539–548.
15 Messersmith WA. NCCN Guidelines Updates: management of metastatic colorectal cancer. *J Natl Compr Canc Netw* 2019; **17**:595–601.
16 Abbas A, Mirza MM, Ganti AK, Tendulkar K. Renal toxicities of targeted therapies. *Target Oncol* 2015; **10**:487–499.
17 Jimenez I, Prado Y, Marchant F, Otero C, Eltit F, Cabello-Verrugio C, *et al*. TRPM channels in human diseases. *Cells* 2020; **9**:E2604.

18 Ferioli S, Zierler S, Zaißerer J, Schredelseker J, Gudermann T, Chubanov V. TRPM6 and TRPM7 differentially contribute to the relief of heteromeric TRPM6/7 channels from inhibition by cytosolic Mg2+ and Mg·ATP. *Sci Rep* 2017; **7**:8806.

19 Zou ZG, Rios FJ, Montezano AC, Touyz RM. TRPM7, magnesium, and signaling. *Int J Mol Sci* 2019; **20**:E1877.

20 Voets T, Nilius B, Hoefs S, van der Kemp AW, Droogmans G, Bindels RJ, Hoenderop JG. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption. *J Biol Chem* 2004; **279**:19–25.

21 Cao G, Hoenderop JG, Bindels RJ. Insight into the molecular regulation of the epithelial magnesium channel TRPM6. *Curr Opin Nephrol Hypertens* 2008; **17**:373–378.

22 Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol* 2007; **18**:2649–2652.

23 Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**:239–45.

24 Yang L, Frindt G, Palmer LG. Magnesium modulates ROMK channel-mediated potassium secretion. *J Am Soc Nephrol* 2010; **21**:2109–2116.

25 Hsieh MC, Wu CF, Chen CW, Shi CS, Huang WS, Kuan FC. Hypomagnesemia and clinical benefits of anti-EGFR monoclonal antibodies in wild-type KRAS metastatic colorectal cancer: a systematic review and meta-analysis. *Sci Rep* 2018; **8**:2047.

26 Shukui Q, Jin L, Liwei W, Jianming X, Ying C, Yuxian B, *et al*. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in patients with RAS wild-type metastatic colorectal cancer: the Open-Label, Randomized, Phase III TAILOR Trial. *J Clin Oncol* 2018; **36**:3031–3039.