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ORIGINAL ARTICLE

Increase in cetuximab-induced skin rash and hypomagnesemia in patients receiving concomitant treatment with proton pump inhibitors (PPIs): a possible drug interaction?

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Abstract

Introduction In a previous study, we found that co-administration of proton pump inhibitors (PPIs) with cetuximab was associated with increased skin toxicity. Both these drugs can induce hypomagnesemia. The aim of this study was to retrospectively explore the possible influence of PPI drugs on cetuximab skin toxicity and the potential synergistic effect of hypomagnesemia.

Patients and methods The files of all eligible patients treated with cetuximab during 2015–2016 with metastatic colorectal carcinoma (mCRC) or head and neck (H&N) carcinoma were reviewed. The concomitant use of PPIs was defined if a drug belonging to that class was included in the patient's chronic medications list.

Results One hundred eighteen patients (61 with H&N carcinoma, 57 with mCRC) were included in the study, and 58 of the 118 patients received PPIs concomitantly with cetuximab. Skin toxicity of any grade was reported in 33/58 (56.9%) patients on PPIs compared with 22/60 (36.7%) patients ($p=0.08$) with grade 3–4 in 19/58 (32.8%) and 2/60 (3.3%), respectively ($p=0.001$). Hypomagnesemia (Mg serum level < 1.2 mg/dL) was reported in 14/58 (25.9%) PPI-treated patients, compared with 5/60 (10.4%) patients not on PPIs ($p=0.08$). Grade 3–4 skin toxicity or hypomagnesemia (Mg < 0.9 mg/dL) was reported in 23/58 (39.7%) patients on concomitant treatment with PPIs, compared with 3/60 (5%) patients not on PPIs ($p=0.001$).

Conclusions Both the rate and the severity of cetuximab-induced skin toxicity and hypomagnesemia were increased by chronic concomitant administration of PPIs. A prospective study is needed to confirm the possible interaction between cetuximab and PPIs.

Keywords Proton pump inhibitors · Cetuximab · Skin toxicity · Hypomagnesemia · Colorectal carcinoma · Head and neck carcinoma

Introduction

Cetuximab is a chimeric IgG1 monoclonal antibody that inhibits epidermal growth factor (EGFR). It is approved for patients who have metastatic colorectal cancer (mCRC) expressing wild-type RAS, a signaling protein in the EGFR pathway or squamous cell cancer of the head and neck. The most common side effect of cetuximab, occurring in over 80% of patients, is an acneiform eruption, with grade 3 or 4 toxicity in over 25% of patients in some studies [1]. This acneiform rash presented in sebaceous areas in the scalp, face and upper trunk with clusters of monomorphic pustular lesions, is usually localized to the hair follicles on sun-exposed areas. The rash related to the high levels of EGFR in the sebaceous glands, thus inhibition of EGFR signaling in the skin causes abnormalities in basal keratinocyte maturation, growth and migration [2]. Studies on cetuximab have shown that patients with a higher-grade acneiform rash have an increase in response rate, time to tumor progression (TTP), and overall survival (OS) [3]. For this reason, severe skin rash is not an absolute contraindication to cetuximab. Grade 2 and higher rashes are associated with a decrease in

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quality of life, low treatment compliance and, in some cases, withdrawal from treatment [4].

Co-administration of PPIs with other drugs could lead to drug–drug interaction, delayed elimination and, potentially, may lead to toxicity if not monitored appropriately. In December 2011, the FDA issued a cautionary warning for the use of high-dose methotrexate therapy in patients on PPIs, citing two cases in which delayed methotrexate metabolism was observed in patients who were undergoing induction dose therapy with 40 mg or more of methotrexate [5].

This delayed metabolism of methotrexate can lead to increased serum levels of methotrexate and its primary metabolite, 7-hydroxymethotrexate. The proposed mechanism for this delayed elimination involves PPI-mediated competitive inhibition of the breast cancer resistance protein [ATP-binding cassette, sub-family G, member 2 (ABCG2)], a low-affinity, high-capacity transporter of methotrexate [6]. One of the earliest studies on the co-administration of PPIs with methotrexate in 76 patients estimated that there was a 27% decrease in the clearance of methotrexate [7].

Another drug interaction is the alteration of pharmacodynamics of the blood-thinning drug clopidogrel (Plavix) by PPI. As a prodrug, clopidogrel requires a biotransformation to be converted into its active form, a process also mediated by the CYP2C19 and CYP3A4 enzymes, as PPI metabolism [8]. This reliance on the same pathway has led to the hypothesis that competition at CYP2C19 may reduce the biological activity of clopidogrel. This is supported by in vitro studies that showed a pharmacodynamic interaction, which was an attenuated antiplatelet effect as measured by adenosine diphosphate–induced platelet aggregation and increased platelet activity [9].

In a previous prospective study that included 33 patients and collected data about chronic medications taken by the study population, 3/5 (60%) patients who used PPIs developed severe skin toxicity, compared to 4/23 (17%) patients who did not use PPIs ($p = 0.057$) [10].

Moreover, although both these drugs can induce hypomagnesemia, the possibility of synergism or an additive effect between them has not been tested yet. There have been several (total, < 50) cases of hypomagnesemia that were associated with long-term PPI use [11–13] and, among the side effects of cetuximab hypomagnesemia has been described. In a retrospective study of 51 patients with metastatic colorectal carcinoma treated with cetuximab, mostly combined with irinotecan-based combination chemotherapy, hypomagnesemia of any grade was detected in 56% of evaluable patients, but grade 3 or 4 hypomagnesemia was observed in 6% and 4% of patients, respectively [14]. In another retrospective study, the charts of 114 patients with colorectal cancer treated with cetuximab were reviewed, and 27% of patients developed grade 3/4 hypomagnesemia. The incidence of grade 3/4 hypomagnesemia was 6%, 23%, and 47% in patients receiving < 3 months, 3–6 months, and > 6 months of cetuximab therapy, respectively. Grade 3/4 hypomagnesemia was refractory to oral supplementation and required daily to 3x weekly intravenous magnesium sulfate supplementation at 6–10 g per dose. Recovery or amelioration in hypomagnesemia occurred approximately 4 weeks after cetuximab discontinuation [15].

In a meta-analysis of incidence and risk of hypomagnesemia with cetuximab for advanced cancer, 19 clinical reports were identified which included a total of 4559 patients available for analysis, with 3081 patients assigned cetuximab-based treatment. This result showed a high incidence of grade 3 and 4 hypomagnesemia (5.6%; 95% CI 3.0–10.2) and a high incidence of all-grade hypomagnesemia associated with cetuximab-based therapy for advanced cancer (36.7%; 95% CI 22–54.4) [16].

The aim of this study was to retrospectively explore the possible influence of PPI drugs on cetuximab skin toxicity and the potential synergistic effect of hypomagnesemia of both drugs.

Patients and methods

This study was approved by the institutional review board of Rambam Health Care Campus (Approval No. 0568-16-RMB). All patients with confirmed RAS-WT mCRC or H&N carcinoma who were treated with cetuximab (Erbitux®) as a single agent or in combination with chemotherapy or radiotherapy during the years 2015 and 2016 were included. Patients were excluded if they previously received cetuximab or had no follow-up after the first cycle of cetuximab.

Treatment schedules

In mCRC patients, cetuximab was administered once a week in a dose of 250 mg per m^2 body surface area (BSA), as a single agent or together with irinotecan, or in combinations with 5-FU and oxaliplatin or irinotecan, every 2 weeks in a dose of 500 mg/m^2 BSA. In H&N patients, cetuximab was administered in locally advanced disease with radiotherapy once a week in a dose of 250 mg per m^2 BSA with a loading dose of 400 mg per m^2 BSA. In the metastatic setting, cetuximab was administered in combination with 5-FU and cisplatin or carboplatin on days 1, 8, 15 every 3 weeks in a dose of 250 mg per m^2 BSA with a loading dose of 400 mg per m^2 BSA.

The files of all patients with mCRC or H&N carcinoma treated with cetuximab in the study period were reviewed. Concomitant use of PPIs was defined if a drug belonging to that class was included in the patient's chronic medications list.

Data collected included age, gender, cancer diagnosis (H&N or mCRC) and stage, performance status, PPI use and magnesium level before treatment with cetuximab and the lowest level of magnesium during treatment. Data were collected from the reported follow-up meetings with the oncologist. The regular reporting included the use of Common Toxicity Criteria of Adverse Events (CTCAE-5) [17], including skin reactions with reporting of onset, distribution, severity, and changes in medication. The patients underwent regular periodic blood tests, including complete blood count and electrolytes (including magnesium level) after each cycle reviewed for the study.

Statistical analysis consisted of determining the frequency count, percentage, median, mean, and standard deviation. Predictive variables were tested with the Chi square and *t* tests. Logistic regression was used to calculate the odds ratios (OR) with 95% confidence intervals (95% CI) and *p* values in bivariate analysis were used to determine associations between patients' characteristics and adverse events (skin rash or hypomagnesemia). Multivariable forward stepwise logistic regression analysis was performed. A multivariate Cox regression analysis was performed. Two-tailed *p* values of 0.05 were considered statistically significant. Statistical analyses were performed using SPSS (Statistics Products Solutions Services) 21.0 software for Windows.

Results

One hundred eighteen patients (77 in 2015, 41 in 2016) were included in the study. Sixty-one patients had H&N carcinoma and 57 patients had mCRC. There were 72 males and 46 females. Mean age was 63 years (range 23–87 years). Forty patients were below age 60, 48 were between age 60–69 years of age, and 30 were over the age of 70. Median follow-up from onset of cetuximab was 12.6 months. Fifty-eight patients received PPIs concomitantly with cetuximab (Table 1).

Skin toxicity of any grade was reported in 33/58 (56.9%) patients on PPIs compared with 22/60 (36.7%) patients not on PPIs ($p = 0.08$) (Fig. 1). Grade 3–4 skin toxicity was reported in 19/58 (32.8%) patients on PPIs compared to 2/60 (3.3%) not on PPIs ($p = 0.001$, HR = 11.88, 95% CI 2.76–51.07) (Fig. 1). Median time to detection of severe skin toxicity was 0.7 months (range 0.2–11.0 months).

Hypomagnesemia (Mg serum level < 1.2 mg/dL) was reported in 14/58 (25.9%) PPIs treated patients compared with 5/60 (10.4%) patients not on PPIs as a chronic medication ($p = 0.08$) (Fig. 2). Median time to detection of hypomagnesemia was 3 months (range 0.4–52.8 months).

Table 1 Demographic and medical characteristics of study sample ($n = 118$)

	No. of patients
Gender	
Female	46
Male	72
Age	
< 60	40
60–69	48
70+	30
Type of cancer	
H&N carcinoma	61
mCRC	57
Performance status (PS)	
0, 1	39
2	16
3 + 4	9
Missing data	54

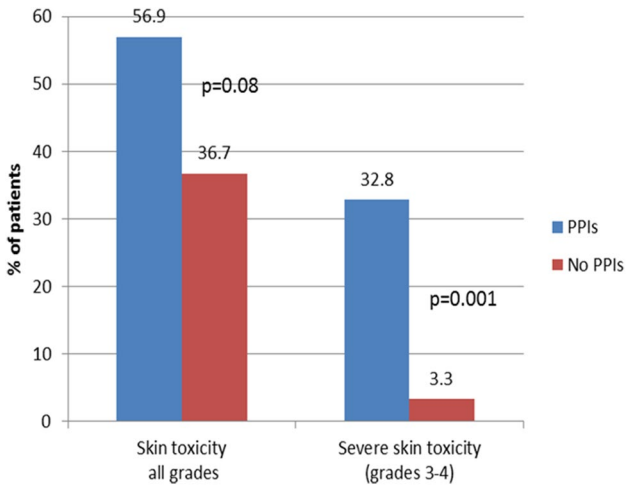

Fig. 1 Grade of skin toxicity among 118 patients on cetuximab treatment with/without chronic use of proton pump inhibitors

Complications of all grade skin toxicity or hypomagnesemia were reported in 40/58 (69%) patients on PPI compared to 23/60 (38.3%) patients not on PPIs ($p = 0.04$, HR = 9.49, 95% CI 1.1–81.52) (Fig. 3). Grade 3–4 skin toxicity or hypomagnesemia (Mg < 0.9 mg/dL) were reported in 23/58 (39.7%) patients on concomitant treatment with PPIs compared with 3/60 (5%) patients not on PPIs ($p = 0.001$, HR = 8.3, 95% CI 2.47–28) (Fig. 3). In multivariate Cox regression analysis, no difference in skin toxicity or hypomagnesemia according to diagnosis, performance status, stage or gender was found. The only significant factor was the use of PPIs medications.

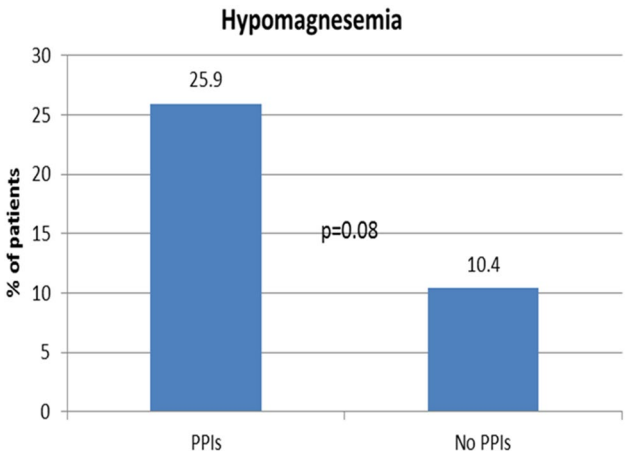

Fig. 2 Grade of hypomagnesemia among 118 patients on cetuximab treatment with/without chronic use of proton pump inhibitors

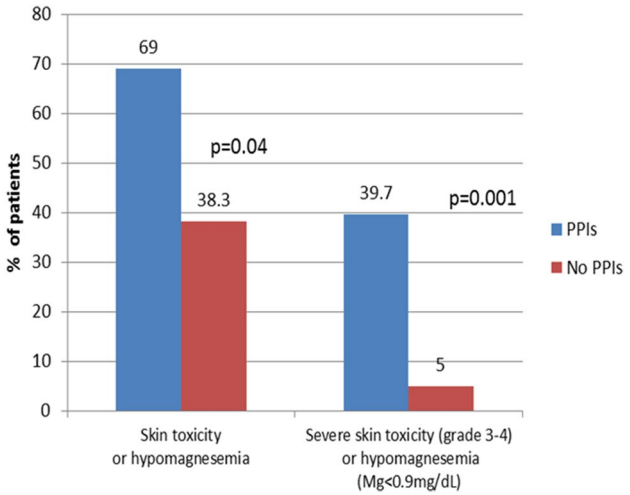

Fig. 3 Combined toxicity of skin rash and hypomagnesemia among 118 patients on cetuximab treatment with/without chronic use of proton pump inhibitors

Discussion

Although the acneiform eruption may demonstrate a positive response to cetuximab, the rash is often uncomfortable with itchiness, burning and pain and can influence quality of life, causing depression, anxiety and social withdrawal, ultimately leading to disruptions in the treatment plan [18, 19]. Predicting severe skin toxicity to cetuximab may help physicians and patients prepare psychologically and physically for the side effects. Currently, there are no predictive factors for cetuximab-induced severe skin toxicity. The only clue came from a prospective study that included over 900 mCRC patients that suggested younger age and men less than 70 years of age are more likely to develop a higher-grade rash with cetuximab, even though the absolute risk of severe rash was low (< 10%) [20]. In the current study, there was no difference in the rate and severity of cetuximab-induced skin toxicity according to age or sex.

The mechanism of increased cetuximab skin toxicity with the concomitant use of PPI is unknown. Cetuximab distribution is independent of dose and approximates plasma volume (2–3 L/m^2) and elimination is via EGFR binding on a large number of tissues (liver and skin), following internalization of the antibody–EGFR complex. The elimination half-life is 3–7 days [21]. Omeprazole distribution is highly related to protein binding (95–96%). The drug is primarily bound to serum albumin and alpha-1-acid glycoprotein. Omeprazole distributes rapidly to extravascular sites. 30 min after intravenous administration in rats, the highest concentration (12–23 nanomole/g tissue) was found in the liver, kidneys and duodenum.

In a case report reported in 2016 [22], a 74-year-old female patient developed skin rashes on the chest and right lower limb and foot 28 days following treatment initiation of PPIs. The skin rashes spread and ulcerated after 3 days and were associated with tracheal mucosal injury and hemoptysis. Treatment of the patient with PPIs was terminated, after which the tracheal hemoptysis and skin rashes markedly improved. In this case, PPIs may have induced exfoliative dermatitis, due to hepatic ischemia, hypoxia and acute renal failure, which may have decreased the metabolism of PPIs, resulting in the accumulation of PPI metabolites.

PPIs metabolism in the liver is extensive. Insignificant amounts of unchanged drug are eliminated via the kidneys or stools. However, a major enzyme involved in the metabolism of omeprazole is the polymorphically expressed cytochrome P450 (CYP) isoform S-mephenytoin hydroxylase, also known as CYP2C19. The elimination of omeprazole is primarily by renal excretion, most of the dose (i.e., 77%) is excreted in the urine in the form of 6 metabolites or more. Biliary elimination of omeprazole following intravenous and oral administration has ranged from 16 to 19% [23]. It is known that PPIs yield a median gastric pH > 5, which would be predicted to significantly reduce erlotinib and other tyrosine kinase inhibitors (TKIs) dissolution and absorption (a 46% decrease in the median erlotinib area under the curve (AUC) with PPIs and a 33% decrease with H2 antagonists in healthy volunteers) [24]. We hypothesize that the concomitant use of PPI altered the metabolism of EGFR inhibitors and interacted with the distribution and elimination phase of cetuximab; a pharmacokinetics study of cetuximab with and without concomitant use of PPI will be conducted in the near future to understand the underling mechanism.

Magnesium balance is tightly regulated through intestinal and renal absorption and excretion, as well as exchange with bone. Only 15–25% of the filtered magnesium is

passively reabsorbed in the proximal tubule. The thick ascending limb of the loop of Henle seems to be the major site of magnesium transport, where the reabsorption of 60–70% of the ultrafiltrate magnesium takes place [25]. Hypomagnesemia may be due to inadequate intake, increased entry to cells, as well as gastrointestinal or renal losses [26]. Among the side effects of cetuximab, hypomagnesemia has been described. It was proposed to relate to EGFR strong expression in the kidney, particularly in the ascending limb of the loop of Henle where 70% of filtered magnesium is reabsorbed, and EGFR blockade may interfere with magnesium transport [27].

There have been several (total, < 50) cases of hypomagnesemia that were associated with long-term PPI use [11–13]. The patients generally presented with profound hypomagnesemia and typically required hospitalization. In approximately 25% of these cases, the patients had persistent hypomagnesemia despite supplements. Prompt resolution of magnesium levels was evident after discontinuance of the PPIs and, in a few cases in which the patients were re-challenged with a PPI, the hypomagnesemia recurred, suggesting a PPI-related effect. To explain the mechanism of hypomagnesemia, some investigators assessed urinary magnesium excretion and performed diagnostic tests for malabsorption or other gastrointestinal problems. Urinary magnesium was low in all studies, suggesting that renal magnesium handling remained intact with PPI use [28]. Gastrointestinal investigations identified no structural cause of hypomagnesemia or malabsorption syndromes, including sprue [13]. Therefore, it is highly likely that PPI impairs intestinal magnesium absorption. According to these data, we hypothesize that increase in the rate and severity of hypomagnesemia is due to the additive effect between the two drugs with different mechanism (renal loss with cetuximab and impaired intestinal absorption with PPI).

The limitations of the present study are its retrospective nature, missing data about the clinical presentation of skin rashes and hypomagnesemia and how these adverse effects were treated (for example, topical or systemic steroids or antibiotics for skin rash and referrals to dermatologist). In addition, whether PPIs increased the rate and severity of other side effects is unknown and should be investigated.

In conclusion, both the rate and the severity of cetuximab-induced skin toxicity and hypomagnesemia were increased by chronic concomitant administration of PPIs in retrospective analysis. A prospective study is needed to confirm the possible interaction between these drugs and to investigate the underlying mechanism. Nevertheless, caution is recommended when given cetuximab to patients with the chronic use of PPI medications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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