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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Background: Proton pump inhibitors (PPIs) may interact with several orally administered drugs, possibly by raising gastric pH levels, leading to altered dissolution and absorption. In a previous study, we found that co-administration of PPIs with cetuximab was associated with increased skin toxicity. To confirm this preliminary observation, we tested this observation retrospectively. Since both these drugs can induce hypomagnesemia, the possibility of synergism between them was also tested.

Methods: The files of patients with metastatic colorectal carcinoma (mCRC) or head and neck (H&N) carcinoma treated at our center with cetuximab as a single agent or in combination with chemotherapy or radiotherapy were reviewed. All eligible patients treated with cetuximab during 2015 and 2016 were included in the study. 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. Median follow-up from onset of cetuximab was 12.6 months [range, 0.5-63.2 months]. Fifty-eight 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 not on PPIs (p = 0.08). 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). 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). Median time to detection of hypomagnesemia was three months [range, 0.4-52.8 months]. 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). Grade 3-4 skin toxicity or hypomagnesemia (Mg < 0.9mg/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).

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.

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