Management of Anti-EGFR-Targeting Monoclonal Antibody-Induced Hypomagnesemia

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By Marwan G. Fakih, MD [3]

Targeting the epidermal growth factor receptor (EGFR) has proven to be of clinical benefit in the management of metastatic colorectal cancer (mCRC). While the use of small-molecule tyrosine kinase inhibitors in this setting has not shown any significant activity and has been associated with increased gastrointestinal toxicity when combined with chemotherapy, a different picture has emerged with the use of EGFR-targeting monoclonal antibodies.

Cetuximab (Erbitux), a chimeric immunoglobulin (Ig)G1 monoclonal antibody targeting EGFR has single-agent activity producing response rates of 6% to 12%[4,5] and results in an improvement in overall survival compared to best supportive care in patients with chemotherapy-resistant mCRC.[5] The combination of cetuximab and irinotecan (Camptosar) in irinotecan-resistant mCRC improves the overall response rate (RR) and progression-free survival (PFS) compared to cetuximab alone.[4]

Furthermore, the integration of cetuximab in first- and second-line irinotecan-based chemotherapy has recently been shown to result in improvements in RR and PFS compared to chemotherapy alone.[6,7]

Panitumumab (Vectibix), a human IgG2 monoclonal antibody targeting the EGFR has also been investigated extensively in mCRC. Similar to cetuximab, panitumumab decreases the risk of progression in comparison to best supportive care in patients with chemotherapy-resistant mCRC.[8] However, this agent has been associated with a significant increase in the risk of severe toxicities when combined with oxaliplatin (Eloxatin) or irinotecan-based combination chemotherapy in the first-line treatment of mCRC.[9] Furthermore, the addition of panitumumab to oxaliplatin-based first-line combination chemotherapy resulted in a worsening in PFS and overall survival compared to chemotherapy alone.[9]

Thus, current clinical data support the use of cetuximab alone or in combination with irinotecan-based therapy in irinotecan-resistant patients, whereas panitumumab use should be limited to single-agent administration in patients who have failed chemotherapy and who cannot tolerate irinotecan plus cetuximab after irinotecan failure. The integration of cetuximab in the first- or second-line settings in combination with irinotecan or oxaliplatin-based combinations to improve the chances of downstaging or to delay disease progression is supported by randomized clinical trials—which will likely result in the increased use of this agent in earlier settings in mCRC. This will undoubtedly result in an increase in toxicities associated with the prolonged use of cetuximab, such as hypomagnesemia.

Incidence

Grade 3/4 hypomagnesemia has been consistently reported across clinical trials of cetuximab and panitumumab. The National Cancer Institute of Canada (NCIC) CO.17 study randomized patients to receive single-agent cetuximab vs best supportive care. The incidence of grade 3/4 hypomagnesemia among cetuximab-treated patients (n = 288) was 5.8% vs 0% in the best supportive care arm.[5] In another randomized study—the Erbitux Plus Irinotecan in CRC (EPIC) trial—of irinotecan plus cetuximab vs irinotecan after therapy with oxaliplatin and fluoropyrimidine had failed, the incidence of grade 3/4 hypomagnesemia was 3.3% for the cetuximab based combination vs 0.4% in the irinotecan arm.[6] In the CRYSTAL study, which randomized patients to receive irinotecan, fluorouracil (5-FU), and leucovorin with or without cetuximab, the incidence of grade 3/4...
hypomagnesemia was 1.8% in the cetuximab-based arm vs 0.2% in the chemotherapy-only arm.[7] However, neither the EPIC nor CRYSTAL study mandated monitoring of magnesium levels in enrolled patients. In fact, only 20% of patients in the CRYSTAL study had a magnesium level drawn sometime during treatment. This explains the lower rate of hypomagnesemia noted in the first- and second-line studies in comparison with the NCIC study, where patients were exposed to considerably shorter durations of treatments with cetuximab.

Other data clearly point to a direct relationship between the duration of cetuximab exposure and hypomagnesemia. In a study of 114 patients at Roswell Park Cancer Institute, we have reported grade 3/4 hypomagnesemia in 5%, 23%, and 47% of patients receiving < 3 months, 3 to 6 months, and > 6 months of cetuximab, respectively.[10] In a prospective study of 98 patients treated with EGFR-targeting monoclonal antibodies with or without chemotherapy, Tejpar reported no grade 3/4 hypomagnesemia in patients receiving < 3 months of treatment, whereas patients receiving 3 to 6 months or > 6 months experienced grade 3/4 hypomagnesemia rates of 3% and 12%, respectively.[11]

These data clearly suggest a cetuximab treatment duration-dependent risk for severe hypomagnesemia. It is therefore expected that the true rate of grade 3/4 hypomagnesemia might have been considerably higher in the EPIC and CRYSTAL studies had magnesium level monitoring been mandated in all patients.

Similar risks of hypomagnesemia are seen with panitumumab treatment. In a randomized study of panitumumab vs best supportive care, 36% of 229 patients receiving panitumumab had some decline in magnesium levels, but only 3% developed grade 3/4 hypomagnesemia.[8] When combined with 5-FU, oxaliplatin, and leucovorin, panitumumab was associated with only a 4% incidence of grade 3/4 hypomagnesemia in the first-line treatment of mCRC.[9] The low frequency of hypomagnesemia was likely related to the lack of stringent guidelines for magnesium monitoring.[9] It is likely that more will be learned regarding the cumulative risk of hypomagnesemia as data matures from the Cancer and Leukemia Group B (CALGB) 80405 trial, which is randomizing patients with untreated mCRC to receive combination chemotherapy with cetuximab, bevacizumab (Avastin), or both. Based on the current data, however, it is likely that the risk of hypomagnesemia exceeds 50% but the risk of grade 3/4 hypomagnesemia ranges from 6% to 17%.[12]

Mechanisms
In a prospective study of patients receiving anti-EGFR monoclonal antibodies, Tejpar et al evaluated serial serum and urine magnesium levels.[11] Although grade 3/4 hypomagnesemia occurred in only 6% of the overall population, a decline in serum magnesium levels occurred in almost all patients. Urine testing confirmed that magnesium wasting was the causative etiology of hypomagnesemia and that this defect was related to a direct effect of monoclonal antibodies on the distal convoluted tubule. Furthermore, the degree of magnesium wasting exhibited a high degree of interpatient variability and tended to worsen with time. There are currently no known prophylactic measures that may prevent this EGFR monoclonal antibody toxicity.

Risk Factors
The most important risk factor for hypomagnesemia in patients receiving EGFR-targeting monoclonal antibody is the duration of treatment, with severe hypomagnesemia sometimes occurring more than 6 months after treatment initiation. Other risk factors that have been reported include a patient's age and the baseline magnesium level. Elderly patients are more susceptible to this toxicity. Interestingly, patients with higher baseline magnesium levels tended to have more pronounced magnesium wasting.[11]

Management
Grade 1/2 Hypomagnesemia
Most hypomagnesemia toxicities associated with cetuximab or panitumumab are grade 1/2 (0.9 mg/dL up to the lower limit of normal), with grade 3 (0.7–0.8 mg/dL) or grade 4 (≤ 0.6 mg/dL) toxicities seen in about 6% to 17% of patients. No evidence suggests that a replacement strategy is necessary for grade 1 hypomagnesemia, as these patients are typically asymptomatic.

For patients with grade 2 hypomagnesemia, we have followed a strategy of weekly intravenous replacement (4 g of magnesium sulfate) for patients with magnesium levels of 0.9 to 1.0 mg/dL. We have attempted oral magnesium supplementation in this population and found this practice to be ineffective and poorly tolerated due to diarrhea.[10] The inefficiency of oral supplements has been similarly confirmed by other groups.[11] One may also consider weekly magnesium monitoring
without replacement for grade 2 hypomagnesemia in asymptomatic patients without cardiac history or cardiac risks—only after an appropriate physician-patient discussion.

Grade 3/4 Hypomagnesemia

Patients with grade 3/4 hypomagnesemia should receive appropriate replacement. These patients are often symptomatic with fatigue, cramps, or somnolence.[11] Many patients do not complain of hypomagnesemia symptoms as they tend to attribute them to cytotoxic chemotherapy, but patients treated at our institute experienced improvement in energy level and performance status after their grade 3/4 hypomagnesemia was reversed. Other reasons for aggressive replacement in patients with grade 3/4 hypomagnesemia include the risk of cardiac arrhythmias. Indeed, cases of sudden death have been reported on some studies of cetuximab and radiation therapy.[12] Whether death in these cases was related to hypomagnesemia is unclear.

Magnesium replacement in patients with severe, grade 3/4 hypomagnesemia can be very challenging. Weekly intravenous replacement is typically inadequate, as serum magnesium levels tend to fall back to the low baseline level within 3 to 4 days. Our experience suggests that these patients require about 6 to 10 g of magnesium sulfate daily to twice weekly, dependent on the patient. An initial strategy of IV replacement and every-other-day serum magnesium monitoring is helpful to guide the frequency of replacement until a steady state is reached. In some patients, magnesium wasting worsens despite ongoing replacement. We have treated a case of ongoing grade 4 hypomagnesemia despite daily 10-g magnesium sulfate replacement.

It is important to note that an aggressive replacement strategy may be associated with significant patient inconvenience. For example, a magnesium sulfate dose of 8 g will require an infusion time of 4 hours, which can be socially limiting when administered on a daily basis. Furthermore, frequent intravenous infusions will require central venous accessing, which may increase the risk of infections.

An alternative strategy for patients requiring frequent magnesium sulfate infusion, if they do not have a large tumor burden, may be to consider a stop-and-go approach to anti-EGFR monoclonal antibody therapy. Usually, serum magnesium levels correct within 6 weeks of stopping cetuximab. The rechallenge of patients with cetuximab after reversal of magnesium wasting (4–8 weeks after a cetuximab break) usually does not result in reoccurrence of grade 3/4 hypomagnesemia before another 6 to 8 weeks. Thus, a 2-month stop-and-go approach may decrease or eliminate the need of magnesium replacement in patients with severe cetuximab-induced hypomagnesemia. We have found this approach to be successful in several patients with grade 4 hypomagnesemia.

—Marwan Fakih, MD

Disclosures:
Dr. Fakih has received honoraria from ImClone for educational activities.

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