Original Article

Cetuximab-induced hypomagnesaemia aggravates peripheral sensory neurotoxicity caused by oxaliplatin

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ABSTRACT

Calcium and magnesium replacement is effective in reducing oxaliplatin-induced neurotoxicity. However, cetuximab treatment has been associated with severe hypomagnesaemia. Therefore, we retrospectively investigated whether cetuximab-induced hypomagnesaemia exacerbated oxaliplatin-induced neurotoxicity. Six patients with metastatic colorectal cancer who were previously treated with oxaliplatin-fluorouracil combination therapy were administered cetuximab in combination with irinotecan alone or irinotecan and fluorouracil as a second-line treatment. All patients had normal magnesium levels before receiving cetuximab. The Common Terminology Criteria for Adverse Events version 3.0 was used to evaluate the grade of neurotoxicity, hypomagnesaemia, hypocalcaemia, and hypokalemia every week. All six patients had grade 1 or higher hypomagnesaemia after starting cetuximab therapy. The serum calcium and potassium levels were within the normal range at the onset of hypomagnesaemia. Oxaliplatin-induced neurotoxicity occurred in all patients at the beginning of cetuximab therapy, with grade 1 neurotoxicity in five patients and grade 2 in one patient. After cetuximab administration, the neurotoxicity worsened in all six patients, and three progressed to grade 3. Among the three patients with grade 3 neurotoxicity, two required a dose reduction and one had to discontinue cetuximab therapy. A discontinuation or dose reduction in cetuximab therapy was associated with exacerbated oxaliplatin-induced neurotoxicity due to cetuximab-induced hypomagnesaemia in half of patients who had previously received oxaliplatin. Therefore, when administering cetuximab after oxaliplatin therapy, we suggest serially evaluating serum magnesium levels and neurotoxicity.

KEYWORDS

hypomagnesaemia; cetuximab; oxaliplatin; neurotoxicity; colorectal cancer


Introduction

Oxaliplatin (L-OHP)-fluoropyrimidine combinations are widely used in the first-line treatment for metastatic colorectal cancer (1-3). Due to recent advances in molecular targeted therapies, cetuximab (Cmab), an anti-epidermal growth factor receptor (EGFR) antibody, is recommended as the first-line therapy with L-OHP, leucovorin, and fluorouracil (FOLFOX) or as second-line therapy after a FOLFOX regimen for stage IV colorectal cancer patients (4,5).

Peripheral sensory neurotoxicity (PSN) is a dose-limiting toxicity that is associated with L-OHP, which is the key drug in the FOLFOX regimen. Therefore, a stop-and-go approach has been proposed to manage PSN (6). PSN can either be transient and acute or chronic due to the accumulation of L-OHP (2,7). The hallmarks of PSN are dysesthesia and paresthesia in the limbs, which are triggered by cold exposure and in some cases accompanied by cramps (8). PSN occurs in 90% of patients who receive L-OHP and persists in 30% of patients after one year of stopping treatment (1). In addition, L-OHP must be discontinued...
when the cumulative dose reaches 800 mg/m² because 10-15% of cases develop grade 3 or higher functional disorder (1,9).

Previous studies on the mechanism of PSN reported that calcium and magnesium replacement effectively reduced chronic PSN, suggesting that these supplements are efficacious (10,11). Moreover, the prospective CONCePT study confirmed the effectiveness of calcium and magnesium replacement (12). However, Cmab has been reported to induce hypomagnesaemia (13-15). This anti-EGFR antibody blocks EGFR in the nephron and inhibits magnesium reabsorption from the convoluted distal tubule, leading to magnesium loss from the kidneys (13-15). Therefore, we retrospectively investigated whether Cmab-induced hypomagnesaemia exacerbated the chronic neurotoxicity associated with L-OHP therapy.

Methods

This study included six patients with unresectable metastatic colorectal cancer who had previously received FOLFOX as a first-line treatment until disease progression and were treated with Cmab in combination with irinotecan alone or irinotecan-fluoropyrimidine combination as a second-line treatment. None of the patients had KRAS codon 12 and 13 mutations in the tumor tissue or diabetes mellitus. The present study was conducted in accordance with the Declaration of Helsinki for the care for human study adopted by the ethics committee of Asahikawa Medical University and Higashi-Asahikawa Hospital. All patients provided written, informed consent.

Patients received Cmab (initial dose of 400 mg/m² infused over 2 hours, and 250 mg/m² weekly over 1 hour thereafter) after receiving 1 hour of irinotecan (150 mg/m²) alone or in combination with fluorouracil, leucovorin, and irinotecan FOLFIRI (150 mg/m² irinotecan infused on day 1 over 2 hours; 200 mg/m² leucovorin infused over 2 hours, followed by fluorouracil given as a 400 mg/m² intravenous bolus and then 2400 mg/m² continuously infused over 44 hours on days 1 and 2) or Cmab alone until the occurrence of progressive disease or unacceptable toxicity. Adverse events were recorded during treatment. Serum magnesium, calcium, and potassium levels were assessed at baseline (i.e., within 1 week before starting Cmab treatment) and then every week thereafter. The Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was used to evaluate the grade of neurotoxicity, hypomagnesaemia, hypocalcaemia, and hypokalemia. Additionally, the following variables were evaluated: 1. total L-OHP dose (mg/m²), 2. time (days) from the last L-OHP dose to first Cmab treatment, 3. cumulative Cmab dose at the onset of hypomagnesaemia, 4. duration (day) and number of Cmab cycles until the onset of hypomagnesaemia, 5. cumulative dose of Cmab at the time of neuropathy aggravation, 6. number of Cmab cycles until neuropathy aggravation, 7. severity of hypomagnesaemia, hypocalcaemia, and hypokalemia at the time of neuropathy aggravation, 8. grade of neuropathy at the time of aggravation, 9. whether Cmab was discontinued or reduced after the neurotoxicity worsened, 10. whether magnesium sulfate was administered, and 11. whether any patients developed diabetes.

Results

Table 1 shows the characteristics of the six patients who were primarily treated with L-OHP-fluoropyrimidine combination therapy for metastatic colorectal cancer and then secondarily treated with Cmab-irinotecan combination therapy. The mFOLFOX6 regimen was administered to all patients, and the median total dose of L-OHP was 722.5 mg/m² (320-1105). The median age at the time of the initial Cmab therapy was 67.5 years (59-80), and the median time between the last L-OHP administration and first Cmab administration was 232 days (202-1046). Grade 1 or higher hypomagnesaemia was observed in all six patients after starting Cmab therapy, although all patients had normal magnesium levels before starting cetuximab. The serum calcium and potassium levels were within the normal range at the onset of hypomagnesaemia. The cumulative dose, median duration, and number of cycles of Cmab at the onset of hypomagnesaemia were 1400 mg/m² (900-1650), 6 days (29-42), and 5 cycles (4-6), respectively. Among the six patients with hypomagnesaemia, five were treated with 1 mEq/mL of magnesium sulfate.

All patients experienced mFOLFOX6 regimen-induced peripheral neuropathy at the beginning of Cmab therapy, with grade 1 neuropathy in five patients and grade 2 neuropathy in one patient. After Cmab administration, PSN worsened in all six patients, and three patients progressed to grade 3. Among the three patients with grade 3 PSN, two required a dose reduction and one had to discontinue treatment. The cumulative dose, median duration, and the number of cycles of Cmab at the time of PSN exacerbation were 2150 mg/m² (1150-3150), 59.5 days (29-105), and 8 cycles (4-12), respectively. Five of the six patients (83%) developed hypomagnesaemia prior to PSN progression. Among these five patients, one had hypokalemia but none had abnormal calcium and potassium levels. One patient (17%) whose PSN was exacerbated before the onset of
**Table 1** Characteristics of six patients who were treated with oxaliplatin-fluoropyrimidine combination therapy for metastatic colorectal cancer followed by a combination of Cmab-irinotecan as a secondary treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Total dose of L-OHP (mg/m²)</th>
<th>Duration (day)</th>
<th>Grade of CTCAE</th>
<th>Treatment for HypoMg</th>
<th>Treatment after at starting worse neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>M</td>
<td>60</td>
<td>1400 (5)</td>
<td>35</td>
<td>105</td>
<td>Mg 1400 (5)</td>
<td>done</td>
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<tr>
<td>2</td>
<td>65</td>
<td>F</td>
<td>76</td>
<td>1400 (5)</td>
<td>29</td>
<td>35</td>
<td>Mg 1400 (5)</td>
<td>done</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>76</td>
<td>1400 (5)</td>
<td>42</td>
<td>105</td>
<td>Mg 1400 (5)</td>
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<td>4</td>
<td>61</td>
<td>F</td>
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<td>Mg 1400 (5)</td>
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<td>5</td>
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<td>M</td>
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<td>Mg 1400 (5)</td>
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</tbody>
</table>

L-OHP, oxaliplatin; Cmab, cetuximab; HypoMg, hypomagnesaemia; CTCAE, The Common Terminology Criteria for Adverse Events version 3.0.

Hypomagnesaemia had normal calcium and potassium levels.

**Discussion**

In the MOSAIC study, 90% of the neurotoxic effects occurred during active L-OHP therapy and the incidence decreased over time after discontinuation. Up to 70% and 80% improvement was noted after one and two years of discontinuation, respectively, which means that 20-30% did not even have improvement (1). Although precise mechanisms underlying the development of PSN have not been fully clarified, PSN has been attributed to the accumulation of platinum in the dorsal root ganglion based on the results from animal experiments (8). Gamelin et al. suggested that a possible mechanism may be the effect of oxalate, one of the breakdown products of L-OHP, on neuronal sodium channels (11). Based on this hypothesis, chelation of oxalate can be a possible candidate for improvement of PSN. For this reason, L-OHP therapy is proactively supplemented with calcium and magnesium for chelation of oxalate. Therefore, administering hypomagnesaemia-inducing Cmab to patients who have been treated with L-OHP over a long period is thought to aggravate PSN by depleting magnesium that is necessary to chelate the breakdown products of accumulated L-OHP. Furthermore, long-term Cmab therapy has been reported to influence not only magnesium levels but also the levels of calcium, potassium, and other electrolytes (9,14-16). These results suggest that hypomagnesaemia may not be the only causative etiology. In our patients, low serum magnesium exacerbated peripheral neuropathy, but the neuropathic symptoms improved with IV magnesium sulfate. Therefore, we postulate that hypomagnesaemia may be pivotal in aggravating peripheral neuropathy. However, patients whose neuropathy worsened before the onset of hypomagnesaemia did not necessarily have abnormal calcium and potassium levels. More studies are needed to investigate the role of other causative factors besides an electrolyte imbalance.

There are several reports on the timing of Cmab-induced hypomagnesaemia. Despite the high degree of interpatient variability, these reports show a correlation between the severity and onset of hypomagnesaemia after a median of 3 months (1-6) for grade 2 and 5.5 months (1-14) for grade 3. Furthermore, additional data clearly indicate a relationship between the duration of Cmab exposure (<3 months, 3 to 6 months, or >6 months) and the incidence/grade of hypomagnesaemia (9,15). In our study, hypomagnesaemia appeared within 5 cycles and approximately one month after initiating Cmab therapy; the neurotoxicity worsened...
after a median of 8 cycles and approximately 2 months of therapy. Except for one patient, exacerbated neuropathy occurred in all patients after a median of 3 cycles and within one month after the onset of hypomagnesaemia. Aside from one patient, all patients had grade 1 hypomagnesaemia when the neurotoxicity began to worsen. Therefore, it is important to monitor serum magnesium levels shortly after initiating Cmab therapy. Based on our results, we were unable to draw any conclusions regarding the relationship between calcium/potassium levels and exacerbated neurotoxicity.

Although most patients with grade 1 and grade 2 hypomagnesaemia after Cmab therapy are asymptomatic, those with grade 3 or higher may present with fatigue or hypocalcaemia (14). For the latter cases, the current recommendation is to measure and correct the magnesium levels if they are low (9); however, the decision to treat low magnesium remains inconclusive (17,18). That is, if the decreased QOL due to hypomagnesaemia outweighs the clinical benefits, the magnesium imbalance should be treated. If, on the other hand, the anticancer effects override the hypomagnesaemia, then low magnesium should be treated less vigorously. In our study, we discontinued Cmab if hypomagnesaemia progressed, but also noted that magnesium wasting could be resolved within 2 weeks (unpublished data). The recovery rate of less than 4 weeks is consistent with the half-life of Cmab (9).

Based on extant reports, the incidence of Cmab-induced hypomagnesaemia is approximately 50% after accounting for all reported grades (19). However, contrary to our study protocol, most studies did not measure magnesium on a weekly basis, raising the possibility that the incidence of hypomagnesaemia is underestimated, especially for grade 1 (9). L-OHP-induced neurotoxicity was aggravated in our study, albeit in a small sample size, with the onset of grade 1 hypomagnesaemia. Therefore, the early detection of hypomagnesaemia is essential and should be factored into the design of large-scale, controlled studies in the future.

Conclusion

Although our retrospective analysis was based on a small sample size, we found that Cmab, as a second-line therapy in patients with long-term L-OHP exposure, may exacerbate residual L-OHP-induced neurotoxicity by inducing hypomagnesaemia. Therefore, we recommend serially evaluating serum magnesium levels and neurotoxicity when initiating Cmab treatment after L-OHP therapy.
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