Incidence of hypomagnesaemia in colorectal and head & neck cancer patients receiving endothelial growth factor receptor (EGFR) inhibitors or platinum agents: a retrospective analysis

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BACKGROUND

- Transport of magnesium (Mg) in the distal convoluted tubule occurs through a Mg permeable channel called TRPM6 and is regulated by the epidermal growth factor (EGF) pathway. When patients are giving cetuximab or panitumumab, which are EGFR inhibitors, this leads to insufficient activation of the TPRM6 channel and causes increased fractional excretion of magnesium
- ATP metabolism, muscle contraction and relaxation, normal neurological function and release of neurotransmitters are all magnesium dependent. Magnesium also contributes to the regulation of vascular tone, heart rhythm, platelet-activated thrombosis and bone formation
- Hypomagnesaemia can cause irritability, muscle cramping and spasms, paresthesia, fatigue, and in more severe cases cardiac arrhythmia and coronary artery vasospasms [1]
- With platinum agents e.g. cisplatin, hypomagnesaemia occurs most commonly due to nephrotoxicity, but can also be related to intestinal malabsorption, protracted vomiting or diarrhea [2]
- When patients develop grade 2 or higher (< 0.5mmol/L) hypomagnesaemia the recommendation is to give IV magnesium sulfate supplementation [3]. At the Odette Cancer Centre patients receive either 2g magnesium sulfate IV over 1 hour or 5g magnesium sulfate IV over 3 hours at the discretion of the oncologist
- We hypothesized that patients receiving EGFRs would be at higher risk for developing hypomagnesaemia, especially patients with gastrointestinal tumours receiving combination therapy, due to secondary toxicity (e.g. diarrhea)

DESIGN

- Data was retrospectively collected on patients from January 2009 to February 2016
- All patients received at least 2 cycles/doses of treatment to be eligible for analysis
- In total 378 patients with GI or head & neck cancers were included in the analysis
- Patients receiving cetuximab for GI cancers also received irinotecan in combination
- Patients receiving oxaliplatin for GI cancers received FOLFOX treatment

Table 1: Comparison of patient demographics and treatment cycles across regimens

	Panitumumab (GI)	Cetuximab (HN)	Cetuximab (GI)	Low-Dose Cisplatin (HN)	High-Dose Cisplatin (HN)	Oxaliplatin (GI)
# of patients	55 (33 M : 22 F)	37 (26 M : 11 F)	36 (21 M : 15 F)	76 (59 M : 17 F)	94 (69 M : 29 F)	80 (42 M : 38 F)
# of cycles (doses)	509	296	302	429	282	664
# of cycles Cancelled	61 (12%)	39 (13%)	11 (4%)	42 (10%)	49 (17%)	46 (7%)
# of Missing Mg values	90 / 448 (20%)	46 / 257 (18%)	44 / 291 (15%)	70 / 387 (18%)	22 / 233 (9%)	193 / 618 (31%)
Age (mean)	64 [25-84]	71 [50-89]	59 [26-84]	62 [31-80]	57 [21-76]	63 [33-86]
Dose per cycle (mean)	410mg	LD: 739mg MD: 462mg	LD: 1035mg MD: 868mg	57mg	189mg	143mg

RESULTS

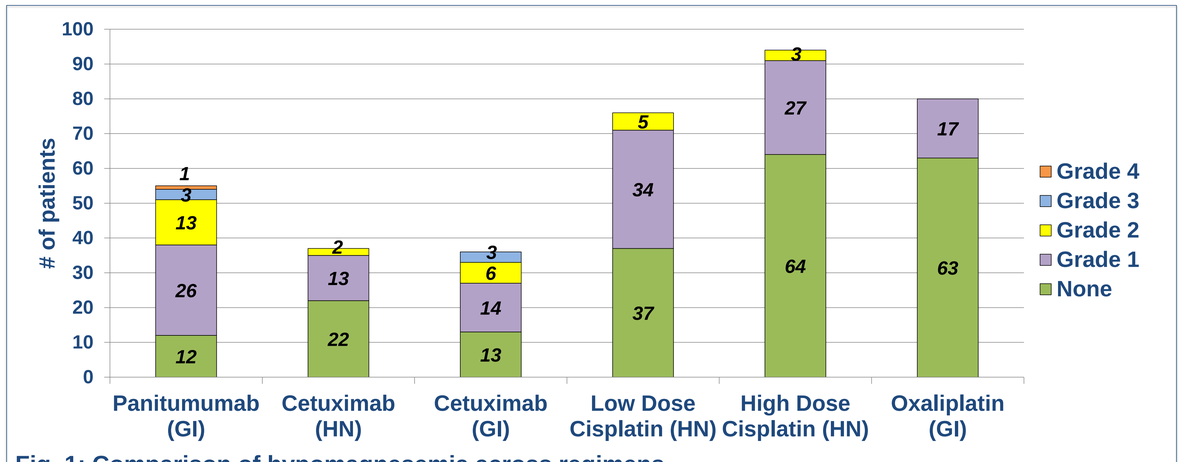

Fig. 1: Comparison of hypomagnesemia across regimens

Grade 1: 0.70 – 0.50mmol/L, Grade 2: < 0.50 – 0.40mmol/L, Grade 3: < 0.40 – 0.30mmol/L, Grade 4: < 0.30mmol/L

RESULTS

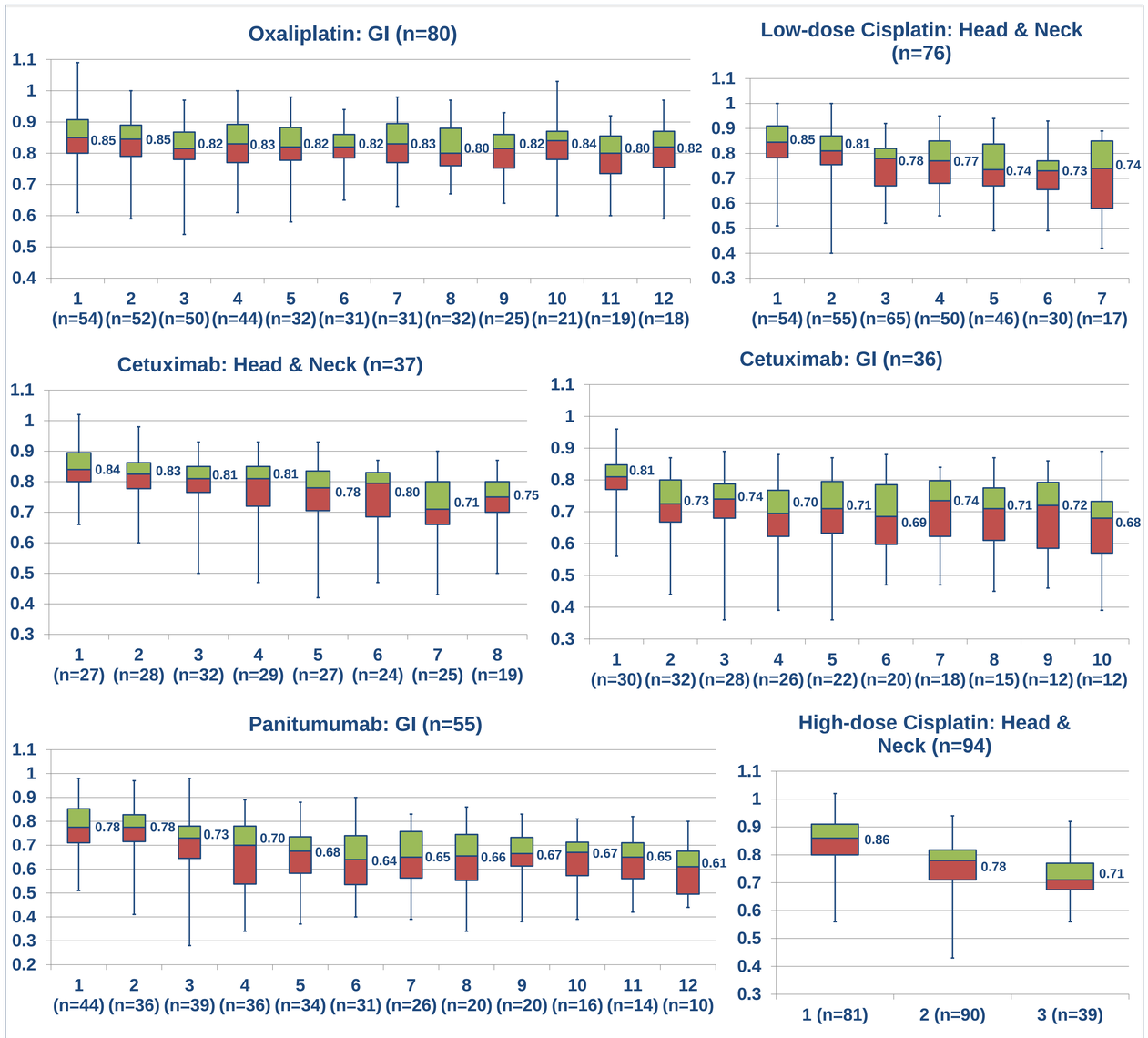

Fig. 2: Regimen and cycle pre-chemo serum magnesium (mmol/L) values

- Cycle 2 change in magnesium from baseline was most significant in high-dose cisplatin patients (-0.10mmol/L) followed by cetuximab GI (-0.08mmol/L), but overall change in magnesium from baseline to final cycle of treatment analyzed was most significant in patients receiving panitumumab (-0.18mmol/L) followed by cetuximab GI (-0.14mmol/L) and high-dose cisplatin (-0.13mmol/L)
- By regimen the order of toxicity from worst to best was:
  Panitumumab > Cetuximab GI > High-dose cisplatin > Low-dose cisplatin > Cetuximab HN > Oxaliplatin
- In total 131 (34%) patients developed grade 1 hypomagnesemia, while 211 (56%) did not develop any hypomagnesemia. Grades 2, 3 and 4 occurred in 29 (8%), 6 (2%) and 1 (<1%) patient(s), respectively

Table 2: Comparison of supplementation across regimens

	Panitumumab	Cetuximab (HN)	Cetuximab (GI)	Low Dose Cisplatin	High Dose Cisplatin	Oxaliplatin	Total
Mg Suppl. Given for Grade 2 or higher	16 / 17 (94%)	2 / 2	9 / 9	4 / 5 (80%)	3 / 3	0 / 0	34 / 36 (94%)
Mg Suppl. Given for Grade 1	6 / 26 (23%)	4 / 13 (31%)	3 / 14 (21%)	14 / 34 (41%)	11 / 27 (41%)	3 / 17 (18%)	41 / 131 (31%)

CONCLUSION

- Due to the retrospective nature of this study we were only able to identify instances of hypomagnesaemia, not the reasoning behind it (i.e. diarrhea, vomiting). We also had no definitive way of knowing if patients were taking oral magnesium supplements on the side
- However, the study findings do support that EGFRs (particularly panitumumab) induce higher grades of hypomagnesemia than either cisplatin or oxaliplatin, especially in the GI setting
- It is important that patients receiving EGFRs or platinum agents have magnesium levels drawn every cycle to avoid low counts that may cause unwanted side-effects or delays in treatment

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