Title of the paper

Delayed Chemotherapy-Induced Nausea and Vomiting in autologous hematopoietic cell transplant patients: an exploratory analysis

Running title

An exploratory analysis on delayed CINV

Authors

Silvia Gonella, MSc, RN[1]; Paola Di Giulio, Associate Professor of Nursing, MSc, RN[1].

[1]Department of Public Health and Paediatric Sciences, University of Torino, Torino, Italy

Correspondence

Silvia Gonella, Department of Public Health and Pediatric Sciences, University of Torino, Via Santena 5 bis,

10126 Torino, Italy

T +39 339 8409093

F +39 011 6705871

silviago87@libero.it

Conflict of interest The authors have no funding or conflict of interest to disclose

Abstract

Purpose: Delayed chemotherapy-induced nausea and vomiting (CINV) continues to be a problem in patients undergoing a hematopoietic cell transplant (HCT) despite progress in antiemetic prophylaxis. The study described the clinical course of nausea and vomiting (NV) and retching over the 5-days following an autologous-HCT in the transplant setting. **Methods:** This longitudinal observational study is an exploratory analysis of data from a trial that assessed the efficacy of aroma in preventing NV related to dimethyl sulfoxide in 69 autologous-HCT patients undergoing high emetogenic chemotherapy (HEC, n = 56) or moderate emetogenic chemotherapy (MEC, n = 13). **Results:** Nausea started to increase on the second day after reinfusion, with a peak between 72 and 96 hours, and decreased on the fifth day. The pattern for vomiting was similar, while retching episodes remained unchanged after the third day following transplant. Nausea and emesis were observed in 73% (n = 41) and 64% (n = 36) of HEC patients, respectively, and in 85% (n = 11) and 62% (n = 8) of MEC patients, respectively. **Conclusion:** Uncontrolled delayed CINV is still a challenge for autologous-HCT patients. Nausea, vomiting and retching are three different symptoms that should be assessed and managed separately in the routine clinical practice.

Key words: Hematopoietic Stem Cell Transplantation; Nausea; Vomiting.

Introduction

The occurrence of chemotherapy-induced nausea and vomiting (CINV) is usually biphasic, consisting of the first 24 hours following chemotherapy (acute CINV) and lasting up to 5-7 days after chemotherapy (delayed CINV) (1). Delayed CINV continues to be an important problem in patients that receive moderate (MEC) to high (HEC) emetogenic chemotherapy.

Lopez-Jimenez et colleagues (2) found that 90% of all patients undergoing autologous or allogeneic hematopoietic cell transplant (HCT) and 55% of acute leukaemia patients treated with multiple-day chemotherapy complained of nausea. In the five days following treatment, approximately 35% of patients with leukaemia and only 10% of HCT patients were completely protected from nausea and vomiting without rescue therapy (2). Our recent randomised controlled trial (3), exploring the efficacy of aroma in preventing nausea and vomiting (NV) related to dimethyl sulfoxide (DMSO) in 69 autologous HCT (auto-HCT) patients undergoing high myeloablative conditioning regimens, found delayed NV in 90% patients.

In spite of the availability of new drugs the problem is still unresolved. Novel classes of antiemetics (e.g., palonosetron, a second-generation 5-hydroxytryptamine-3 receptor antagonist ($5HT_3$-RA) and aprepitant, a neurokinin-1 receptor antagonist (NK1-RA)) improved control of CINV but mainly of emesis and in the acute phase. Schwartzberg and colleagues (4) showed that three quarter of HCT-patients complained of delayed nausea although the use of second generation $5HT_3$-RA. A study on 1143 patients receiving HEC found that over 60% of patients randomised to palonosetron suffered from delayed nausea and almost 40% reported delayed emesis compared to those treated with granisetron plus dexamethasone (5).

A trial (6) on the superiority of aprepitant (n = 260) versus standard therapy (n = 260) in patients receiving high-dose cisplatin, showed that patients who received aprepitant had similar acute and delayed nausea compared to those undergoing standard therapy (27.7% vs 30.9% and 49% vs 52.3%, respectively). Patients with emesis were significantly lower in the aprepitant compared with the standard therapy group, both in the acute and delayed phases (10% vs 20.7% and 19.2% vs 41.2%, respectively). A phase III trial also found that 47% (n = 122) and 28% (n = 73) of patients randomised to aprepitant still complained of delayed nausea and vomiting (7).

The problem is further complicated by a lack of specific guidelines for haematological patients and by a variable compliance with the available guidelines. A recent prospective observational study in eight European countries (8) in 991 chemotherapy-naïve adults undergoing HEC or MEC showed low adherence to antiemetic guidelines, varying between the acute and delayed phases, and emetogenity of regimens. A guideline consistent CINV prophylaxis (GCCP) was implemented for 55% and 46% patients during the acute and delayed phases, respectively, and was lower in HEC compared to MEC regimens (21, 7.3% vs 133, 46.3%), both in the acute and delayed phase. Other studies (9) showed an 11% adherence to the Multinational Association of Supportive Care in Cancer (MASCC) guidelines (10) for the prevention of delayed CINV in 75 HEC patients, with frequent omissions of corticosteroids and an overuse of $5HT_3$-RAs. Poor adherence to dexamethasone and NK1-RA continues to be a widespread problem (11-13).

However, adherence to antiemetic guidelines improved the control of CINV. In two studies (8,13) GCCP-treated patients reported less delayed CINV than those without the recommended prophylaxis. Gilmore and colleagues found patients receiving a

GCCP to have a 31% increase in delayed CINV protection compared to those without the recommended prophylaxis (adjusted odds ratio [OR] = 1.31, 95% CI 1.07-1.69, p = 0.037). A similar although not statistically significant advantage was found by Aapro (OR = 1.27, 95% CI 0.92-1.75, p = 0.142) (8).

Despite many studies (4,14) explored the incidence of acute and delayed CINV associated with high dose conditioning regimens for HCT, none described their daily clinical course in a transplant setting. This study aims to describe the course of nausea, vomiting and retching over the five days following auto-HCT.

Methods

Study design

Longitudinal observational exploratory analysis of data derived from a multicentre RCT that was conducted between June 2012 and January 2013 (3). The patient data were analysed as a merged prospective cohort. The study was approved by the ethics committee.

Primary study

A randomised, three-arm, open-label trial in four Italian large bone marrow transplant centres was conducted. The aim of the primary study was to assess the effectiveness of orange aroma in preventing NV related to DMSO in 69 auto-HCT patients. DMSO is the cryopreservative used to store hematopoietic cells and is indeed associated with frequent NV partly related to its characteristic garlic-like breath (15). The smell and flavor of orange had been hypothesized to reduce the patient's perception of its unpleasant odor (16,17). Patients were randomised to

orange (n = 23) or non-citrus ice lollies (n = 21) and routine treatment (deep breaths, n = 25).

Data on NV and retching were collected up to 5 days after infusion. Patients completed 6-day daily diaries beginning on the transplant day and continuing until day 5, reporting their nausea intensity every 4 hours (Numeric Rating Scale [NRS] 0-100) along with vomiting and retching (VR) episodes.

Exploratory secondary analysis

The aim of this exploratory secondary analysis was to describe the course of nausea, vomiting and retching over the five days following auto-HCT, regardless the treatment received (i.e., orange ice lollies, non-citrus ice lollies, deep breaths) in the primary study. Patients' data were analysed as a merged prospective cohort controlling for the treatment.

Data collection

Data on NV and retching were collected up to 5 days after infusion, meaning an observation period from 2 to 7 days after the end of the conditioning regimen, based only on chemotherapy in this group of patients. The transplant generally takes place 24 hours after the end of chemotherapy (18).

Antiemetic prophylaxis was collected from clinical records. Nausea was considered absent if <5, controlled between 5-25 and uncontrolled if >25 (2). Distinct VR episodes were separated by at least 1 minute. VR were considered controlled if there were ≤2 episodes/day (vomiting or retching) (2).

The emetogenic potential of each drug was defined according to the MASCC guidelines (10).

The emetogenicity of the combined regimens was defined as follows: not increased by the minimal emetogenic agent and increased by one level from the low emetogenic agent compared to the most emetogenic agent administered; the moderately and highly emetogenic agent increased the emetogenicity of each drug by one level (19).

According to MASCC guidelines (10), the following regimens are recommended in the delayed phase: dexamethasone days 2-4 plus aprepitant days 2-3 after chemotherapy for HEC and aprepitant, dexamethasone or a $5HT_3$RA days 2-3 after chemotherapy for MEC.

Adherence to the recommended prophylaxis was scored as yes/no. Patients were classified as receiving GCCP or guideline inconsistent CINV prophylaxis (GICP) if they were given or not the recommended drugs daily, respectively (8).

Data analysis

Descriptive statistics were adopted. Intensity of the nausea was measured over 24 hours and expressed as the median and Inter-Quartile Ranges (IQR), and the episodes of VR were expressed as sums. Categorical variables were summarised as sums and percentages, and Fisher's exact test was used for comparisons.

A correlation structure was specified to account for repeated measures over time (24, 48, 72, 96 and 120 hours after reinfusion) on the same patient. A continuous-time autoregressive of order 1 correlation structure resulted in the best model fit, based on Akaike Information Criterion. We controlled by age, sex, treatment and number of stem cell bags infused. The linear relationship of nausea intensity over time was assessed using restricted cubic splines and was tested with a Wald chi-square test. The data were analysed with R version 2.15 (20). All p-values are two-

sided, and a p-value of less than 0.05 was considered significant.

Results

Over 60% (n = 43) of patients were male, and approximately 80% (n = 56) had HEC. More than half (n = 32) of HEC patients were given a high dose melphalan, whereas all MEC patients were given melphalan at a lower dose. The patient characteristics and treatments administered are shown in table 1.

All patients, except one, received methylprednisolone 125 mg on the transplant day. Before reinfusion, hydrocortisone 200 mg was administered alone in a MEC patient and in combination with methylprednisolone in 15 HEC patients.

Nearly all the patients (93%) received $5HT_3$-RA. Overall, less than 20% received a guideline-recommended antiemetic prophylaxis. Only seven HEC patients received aprepitant, and one patient alone received dexamethasone. No HEC-patients were given prophylactic treatment that was adherent to the MASCC guidelines. In contrast, all MEC patients, except one, received post-chemotherapy prevention for delayed CINV with a $5HT_3$-RA (table 1). Two or more antiemetic agents were administered to 12 (17%) patients.

At the end of the transplant, 51 patients (74%) reported no nausea, 10 reported controlled nausea and 7 reported uncontrolled nausea (information missing for 1 patient).

The course of nausea was similar for HEC and MEC patients, which started to increase on the second day after reinfusion, peaked between 72 and 96 hours, and decreased on the fifth day. Longitudinal regression analyses showed an average increase of 3.8 points in nausea intensity every 24 hours.

The overall pattern for vomiting was similar, while retching episodes remained unchanged after the third day following transplant. The results are summarised in table 2.

During the 5-day observation period, 52 (75%) patients reported nausea and over 60% reported (n=44) vomiting or retching. At least once in the 5 days after transplant, 24 patients (35%) had uncontrolled nausea and 40% (n = 28) had more than two episodes of vomiting or retching. Overall, 32 patients had NV or retching. However, 9 patients experienced emesis or retching without nausea, and 18 (26%) experienced nausea without vomiting or retching. At least once, 41 HEC (73%) and 11 MEC (85%) patients reported nausea, which was uncontrolled in 19 (34%) HEC and in five (38%) MEC patients. Similarly, 36 (64%) HEC and 8 (62%) MEC patients reported emetic episodes (table 3). More MEC patients reported uncontrolled vomiting or retching compared to HEC patients (7, 54% vs 21, 38%), but the emetic episodes per day per patients between the two groups were similar (1.2 vs 1.3).

However, no significant differences were found between the HEC and MEC patients (table 3).

Of 12 patients treated with GCCP, 9 (75%) reported no uncontrolled vomiting or retching episodes vs 32 (56%) in the GICP group, whereas no difference was observed in the control of nausea between patients exposed or not to the recommended prophylaxis. However differences were not significant (p = 1.000, data not shown).

Discussion

This study described the course of NV over the five days following auto-HCT. About 65% of the patients had multiple myeloma and almost all received auto-HCT with

melphalan, that is the treatment of choice in patients younger than 65 years according to a recent consensus statement (21).

We observed a greater incidence of delayed NV compared with previous studies (6,7), possibly due to a longer observation period after the end of the conditioning regimen (7 days vs 5 days) (22,23). Similar to other studies (22,23), we found no significant differences in delayed nausea between HEC and MEC patients. Both studies (22,23) showed that HEC patients had a higher risk of delayed emesis, while no differences were observed in our study for vomiting and retching. However, our MEC subgroup was limited in size and the study did not have enough power for this analysis.

The clinical course of delayed CINV described in this study differs from that portrayed by Bloechi-Daum et al. (22) in their prospective study on 298 naïve patients with different cancers. They showed NV plateauing between days 2 and 3 after chemotherapy and slightly decreasing between day 3 and 4. However, we found the peak on day 6 after the end of the conditioning regimen, with an almost 50% decrease in the nausea intensity on day 7. However, they only included patients receiving single-day chemotherapy, while 35% of our patients received multiple-day chemotherapy, which may explain the delay in reaching the peak.

Our findings highlight the importance of a separate assessment for vomiting and retching because their pathways most likely differ. Vomiting decreased along with nausea, whereas retching remained significantly unchanged when patients had no more matter to expel. Hence, routine assessment of retching may avoid the risk of underestimating the adverse chemotherapy effects. However, 40% of our patients complained of nausea without emesis or vice versa, confirming that the

neurotransmitter pathways of NV are most likely not identical in spite of NV are correlated and their clinical course is similar.

The poor adherence to guidelines for delayed antiemetic prophylaxis limited to HEC patients was already shown in other studies: according to Gomez et al. (11), appropriate administration of NK1-RA was approximately 10%. In addition, dexamethasone was almost never administered, similar to previous studies (8,11,12,24) where administration of corticosteroids ranged between 10-97% of patients, depending on the emetogenic potential of chemotherapy and the line of treatment. However, immunosuppressed transplant patients are at higher risk of infections and steroids were most likely not used to avoid increasing this risk. This may explain the overuse of serotonin antagonists and the higher adherence to the guidelines in MEC regimens compared with HEC regimens because $5HT_3$-RAs represent an alternative to dexamethasone for delayed CINV only in MEC-treated patients. The differences in nausea, vomiting and retching between GCCP and GICP patients cannot be commented as information about the antiemetic regimens as well as the control of CINV during the acute phase was not collected in the main study. The current antiemetic guidelines are aimed only at emesis prevention, and ours as well as Aapro's findings (8), suggest that NV are separate phenomena requiring different remedies. However, other causes, such as mucositis, the preliminary symptoms of which are nausea and abdominal cramps, may have contributed to the increased incidence of NV(25).

These exploratory data analyses were limited by the small sample, which did not allow subgroup comparisons, and antiemetic doses were not recorded. Moreover, the etiology of NV in HCT recipients is multi-factorial and includes damage to the gastrointestinal lining that may result in a continual source of serotonin release, side

effects of prophylactic antibiotics and narcotic analgesics, and the high-dose preparative regimens that lead to a poor end-of-regimen control rate. However, this study contributes to our knowledge of the course of NV and retching in transplant patients who are usually heavily treated and receive multi-days chemotherapy regimens.

In summary, delayed CINV continues to be a challenge for healthcare professionals working with auto-HCT patients despite the progress in antiemetic prophylaxis. In auto-HCT patients, the course of NV differs from other patients receiving chemotherapy, with a delayed peak most likely due to multi-drug regimens. Further studies are warranted to define the best anti-emetic regimen in this population and to explore the control of symptoms in auto-HCT patients treated with GCCP compared to GICP.

Finally, nausea and vomiting were confirmed being two separate entities. Similarly, the retching was shown as a symptom different from vomiting. As not only vomiting but also nausea and retching create discomfort to the patients and impact on their quality of life, all of the three symptoms should be assessed, prevented, and treated separately in the routine clinical practice.

References

1. Ettinger DS, Armstrong DK, Barbour S, et al. Antiemesis: NCCN Clinical practice guidelines in oncology for antiemesis version 1 2012. J Natl Compr Canc Netw. 2012;5(1):12-33.
2. Lopez-Jiménez J, Martin-Ballesteros E, Sureda A, et al. Chemotherapy-induced nausea and vomiting in acute leukemia and stem cell transplant patients: result of a multi-center observational study. Haematologica. 2006;91(1):84-91.
3. Gonella S, Bruno B, Berchialla P, Di Giulio. Are orange lollies effective in preventing nausea and vomiting related to Dymethyl Sulfoxide? A multicenter randomized trial. Support Care Cancer. 2014; 22(9):2417-2424.
4. Schwartzberg LS, Jacobs P, Matsouka P, Azevedo W, Pinto A. The role of second-generation 5-HT_3 receptor antagonist in managing chemotherapy-induced nausea and vomiting in hematological malignancies. Crit Rev Oncol Hematol. 2012; 83(1):59-70.
5. Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol. 2009;10(2):115-124.
6. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of Chemotherapy-Induced Nausea and Vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – The Aprepitant Protocol 052 Study Group. J Clin Oncol. 2003;21(22):4112-4119.

7. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the Neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of Chemotherapy-Induced Nausea and Vomiting. Cancer. 2003;97(12):3090-3098.
8. Aapro M, Molassiotis A, Dicato M, et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). Ann Oncol. 2012;23(8):1986-1992.
9. Burmeister H, Aebi S, Studer C, Fey MF, Gautschi O. Adherence to ESMO clinical recommendations for prophylaxis of chemotherapy-induced nausea and vomiting. Support Care Cancer. 2012;20(1):141-147.
10. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010;21(Suppl 5):232-243.
11. Gomez DR, Liao KP, Giordano S, Nguyen H, Smith BD, Elting LS. Adherence to national guidelines for antiemesis prophylaxis in patients undergoing chemotherapy for lung cancer. A Population-Based Study. Cancer. 2013;119(7):1428-1436.
12. Koch S, Wein A, Siebler J, et al. Antiemetic prophylaxis and frequency of chemotherapy induced nausea and vomiting in palliative first-line treatment of colorectal cancer patients: The Northern Bavarian IVOPAK I Project. Support Care Cancer. 2013;21(9):2395-2402.
13. Gilmore JW, Peacock NW, Gu A, et al. Antiemetic guideline consistency and incidence of Chemotherapy-Induced Nausea and Vomiting in US community oncology practice: INSPIRE Study. J Oncol Pract. 2014;10(1):68-74.

14. Stiff PJ, Fox-Geiman MP, Kiley K, et al. Prevention of nausea and vomiting associated with stem cell transplant: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. Biol Blood Marrow Transplant. 2013;19(1):49-55.
15. Santos NC, Figueria-Coelho J, Martins-Silva J, Saldanha C. Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular and molecular aspects. Biochem Pharmacol. 2003; 65(7):1035-1041.
16. Prior D, Mitchell A, Nebauer M, Smith M. Oncology nurses' experience of dimethyl sulfoxide odor. Cancer Nurs. 2000; 23(2):134-140.
17. Potter P, Eisenberg S, Cain KC, Berry DL. Orange interventions for symptoms associated with dimethyl sulfoxide during stem cell reinfusions. Cancer Nurs. 2011; 34(5):361-368.
18. Cox MA, Kastrup J, Hrubisko M. Historical perspectives and the future of adverse reactions associated with haemopoietic stem cell cryopreserved with dimethyl sulfoxide. Cell Tissue Bank. 2012; 13(2):203-215.
19. Fabi A, Malaguti P. An update on palonosetron hydrochloride for the treatment of radio/chemotherapy-induced nausea and vomiting. Expert Opin Pharmacother. 2013;14(5):629-641.
20. RC Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, 2012. ISBN 3-900051-07-0.
21. Patriarca F, Petrucci MT, Bringhem S, et al. Considerations in the treatment of multiple myeloma: a consensus statement from Italian experts. Eur J Haematol. 2009;82(2):93-105.
22. Bloechi-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately

emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol. 2006;24(27):4472-4478.

23. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer. 2004;100(10):2261-2268.
24. Fuji H, Iihara H, Ishihare M, Takahashi T, Yoshida K, Itoh Y. Improvement of adherence to guidelines for antiemetic medication enhances emetic control in patients with colorectal cancer receiving chemotherapy of moderate emetic risk. Anticancer Res. 2013;33(12):5549-5556.
25. Blijlevens N. Cytotoxic treatment-induced gastrointestinal symptoms. Curr Opin Support. Palliat Care. 2007;1(1):16-22.

Table 1 Patients' characteristics

	All patients (n=69)	**HEC** (n=56)[a]	**MEC** (n=13)[b]
Male (n,%)	43 (62)	34 (61)	9 (69)
Age years (median; IQR)	58 [50.5-62.5]	57.5 [49-62]	62 [57-64.5]
Diagnosis (n)			
MM/LNH/L. Plasmacellular/Other[c]	45/10/5/9	33/10/5/8	12/-/-/1
Antiemetic prophylaxis (n)[d]			
5-HT_3RA	64	52	12
Metoclopramide	9	8	1
APR	7	7	-
Chlorpheniramine	3	3	-
Alizapride	1	1	-
DEX	1	1	-
GCCP (n,%)	12 (17.4)	-	12 (92.3)

APR, aprepitant; BEAM, bendamustine-etoposide-cytarabine-melphalan; Bu-Cy, busulfan-cyclophosphamide; DEX, dexamethasone; D-PACE, dexamethasone-cisplatin-adriblastin-cyclophosphamide-etoposide; FEAM, fotemustine-etoposide-cytarabine-melphalan; 5-HT_3RA, 5-hydroxytryptamine receptor antagonist; LH, Hodgkin's lymphoma; NHL, Non-Hodgkin's lymphoma; LAM, acute myeloid leukemia; MM, multiple myeloma; M-VD, velcade-melphalan-dexamethasone.

[a] Melphalan 200 mg/m^2 (n=32), FEAM (n=14), M-VD (n=4), Bu-Cy (n=3), Ara-C/Idarubicin (n=1), BEAM (n=1), D-PACE (n=1)

[b] All patients received Melphalan 100 mg/m^2

[c] LAM (n=4), LH (n=2), L. Burkitt (n=1), Reticulosarcoma (n=1) in HEC group. M. Waldestrom (n=1) in MEC group

[d] The sum is greater than the total because some patients received multidrug treatment

Table 2 Nausea, vomiting and retching over the five days following autologous transplant

	Time following the transplant day				
	0-24 h	24-48 h	48-72 h	72-96 h	96-120 h
Daily nausea intensity[a] (median [IQR])					
HEC (n=56)	2.8 [0-12.5]	4 [0-16.7]	7.1 [0-20]	9.2 [0-30.8]	6.1 [0-24.7]
MEC (n=13)	0 [0-10.5]	0 [0-13.2]	8.3 [0.5-35.2]	12 [0-44.5]	4.9[0-31.3]
All (n=69)	0.4 [0-12.1]	1.7 [0-16.3]	7.2 [0-20.9]	10 [0-31.5]	5.7 [0-24.3]
Patients with controlled, uncontrolled or no nausea (n) [a,b]					
HEC (n=56)	13/9/34	16/10/30	22/12/22	20/16/20	18/12/26
MEC (n=13)	3/1/9	3/2/8	4/4/5	3/4/6	4/3/6
All (n=69)	16/10/43	19/12/38	26/16/27	23/20/26	22/15/32
Vomiting episodes (N)					
HEC (n=56)	20	29	73	51	33
MEC (n=13)	6	2	9	8	10
All (n=69)	26	31	82	59	43
Retching episodes (N)					
HEC (n=56)	15	29	35	36	35
MEC (n=13)	1	9	11	11	13
All (n=69)	16	38	46	47	48
Patients with controlled vs uncontrolled vomiting or retching or none (n)[c]					
HEC (n=56)	6/4/46	5/10/41	12/14/30	13/14/29	10/14/32
MEC (n=13)	2/1/10	3/1/9	3/3/7	1/2/10	3/2/8
All (n=69)	8/5/56	8/11/50	15/17/37	14/16/39	13/16/40

[a] On Numeric Rating Scale 0-100

[b] No nausea (NRS <5)/controlled (NRS 5-25)/uncontrolled (>25)

[c] Controlled (≤ 2 episodes)/uncontrolled (>2 episodes)

Table 3 Nausea, vomiting and retching over the five days in HEC and MEC patients

	HEC (n=56) N (%)	**MEC (n=13)** N (%)	***p***[d]
At least one episode of			
any nausea[a]	41 (73)	11(85)	1.000
uncontrolled nausea[b]	19 (34)	5 (38)	1.000
At least one episode of			
vomiting or retching	36 (64)	8 (62)	1.000
uncontrolled vomiting or retching[c]	21 (38)	7 (54)	1.000

[a] > 5 on NRS
[b] > 25 on NRS
[c] > 2 episodes
[d] Fisher's exact test