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Adherence to Antiemetic Guidelines in Patients with Malignant Glioma: A Quality Improvement Project to Translate Evidence into Practice

Mary Lou Affronti, DNP, RN, ANP, MHSc^{1,2}, Susan M. Schneider, PhD, RN, AOCN®, FAAN², James E. Herndon II, PhD³, Susan Schlundt, RN, BSN, OCN⁴, and Henry S. Friedman, MD^{1,5}

¹ Department of Surgery, Durham, North Carolina 27710

² Department of Duke University School of Nursing, Durham, North Carolina 27710

³ Department of Biostatistics and Bioinformatics, Durham, North Carolina 27710

⁴ Department of Duke University Health System Technology Services, Durham, North Carolina 27710

⁵ Department of Duke Medicine, Durham, North Carolina 27710

⁶ Department of Duke University Health System, Durham, North Carolina 27710

Abstract

Purpose—A quality improvement project was implemented to improve adherence to evidence-based antiemetic guidelines for malignant glioma patients treated with moderately-emetic chemotherapy (MEC). Poorly controlled chemotherapy-induced nausea and vomiting (CINV) reduce cancer treatment efficacy and significantly impair cancer patients' quality of life (QOL). Review of Duke University Preston Robert Tisch Brain Tumor Center (PRTBTC)'s usual practice demonstrates a high incidence (45%) of CINV, despite premedication with *short-acting* 5-HT₃-serotonin receptor antagonists (5-HT₃-RAs). National Comprehensive Cancer Network (NCCN)'s evidence-based guidelines recommend the combination of the *long-acting* 5-HT₃-RA palonosetron (PAL) and dexamethasone (DEX) for the prevention of *acute and delayed* CINV with MEC. Low adherence (58%) to antiemetic guidelines may have explained our high CINV incidence.

Methods—One-sample, quasi-experimental design evaluated a combination intervention that included a provider education session; implementation of risk-assessment tool with computerized, standardized antiemetic guideline order-sets; and a monthly audit-feedback strategy. Post-implementation adherence to evidence-based antiemetic order-sets and patient outcomes were measured and compared to baseline and historical data. Primary outcome was the guideline order-set adherence rate. Secondary outcomes included nausea/vomiting rates and QOL.

Results—Adherence to ordering MEC guideline antiemetics increased significantly, from 58% to a sustained 90%, with associated improvement in nausea/vomiting. In acute and delayed phases,

Corresponding Author/Address for reprints: Mary Lou Affronti, DNP, RN, ANP, MHSc, The Preston Robert Tisch Brain Tumor Center at Duke, Room 047 Baker House, South Hospital, Trent Drive, Duke University Medical Center, Durham, NC 27710. Phone: (919) 684-5301; Fax: (919) 681-1697; affro002@mc.duke.edu.

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75% and 84% of patients, respectively, did not experience CINV. There was no significant change in QOL.

Conclusion—Combination intervention and audit-feedback strategy to translate evidence into oncology practice improved and sustained adherence to antiemetic guidelines. Adherence corresponded with effective nausea/vomiting control and preserved QOL in patients with malignant gliomas.

Keywords

Chemotherapy; Nausea; Emesis; Chemotherapy-induced nausea and vomiting; Supportive care; Antiemetic guidelines; Evidence-based practice; Gliomas

INTRODUCTION

Glioblastoma is the most lethal type of brain tumor, with a poor median survival of 14.6 months despite standard therapy consisting of surgery, radiotherapy, and concurrent adjuvant chemotherapy [1]. Therefore, quality of life (QOL) through symptom management remains an important goal in the care of these patients. Chemotherapy-induced nausea and vomiting (CINV) rank as the most disturbing side effects of cancer therapy and impact QOL negatively [2]. Studies suggest providers underestimate the incidence of *delayed* CINV (occurring > 24-120 hours post-treatment), and thus inadequately manage CINV [3-5]. Poorly controlled CINV depletes resources and compromises compliance to treatment, leading to decreased treatment efficacy [4].

Duke University's PRTBTC treats approximately 2,000 individuals with gliomas annually. Six physicians and eight advanced practice providers (APPs) make the choices regarding the antiemetic regimens to control the critical side effect of CINV. Providers primarily premedicated with short-acting 5-HT₃-serotonin-receptor antagonist (5-HT₃-RA) antiemetics, which effectively prevent *acute* CINV (occurring within 24 hours post-treatment). However, a major limitation of promising moderately-emetic chemotherapy (MEC) regimens administered within the PRTBTC was the associated high incidence (45%) of CINV or low (55%) complete response (CR) rate [6,7].

In an effort to transform PRTBTC's practice culture and better the prevention of both acute and delayed CINV and improve the QOL of glioma patients, we designed a quality improvement project to increase the adherence of antiemetic ordering to the evidence-based NCCN antiemetic guideline for patients treated with MEC. After an education session and implementation of a risk-assessment tool with computerized, standardized order-sets, we compared adherence and patient outcomes with historical benchmark and baseline data. After this combination intervention, we predicted that providers would adopt a practice change and choose antiemetic order-sets that conform to the NCCN guidelines in order to improve the care of our glioma patients.

BACKGROUND AND SIGNIFICANCE

Prevention of CINV in cancer patients receiving antineoplastic therapy has improved dramatically due to the advent of new antiemetics. While available antiemetics can prevent

70-80% of CINV, 60-80% of patients continue to experience nausea and vomiting [4,8,3,9,10].

Short-acting 5-HT₃-RAs are the most widely used antiemetics in the prevention of *acute* CINV [11-13,4]. However, recently published meta-analyses demonstrate that the newer, long-acting 5-HT₃-RA PAL is superior to other first generation 5-HT₃-RAs in preventing *both acute and delayed* CINV; and both agents have similar, minor side effects [14-16]. When compared to patients receiving short-acting 5-HT₃-RAs, patients receiving PAL had less nausea (acute-fixed effect: RR=0.86; 95% CI: 0.76, 0.96, $P=0.007$; delayed: RR=0.85; 95% CI: 0.78, 0.93, $P<0.0003$) [15]. Patients also had less vomiting (acute-fixed effect: RR=0.79; 95% CI: 0.68, 0.91, $P=0.001$; delayed RR=0.78; 95% CI: 0.70, 0.87, $P<0.00001$) [15]. This meta-analysis was the basis for the high-grade, evidence-based NCCN, Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) antiemetic guidelines for MEC. The NCCN/MASCC/ASCO guidelines currently recommend the combination of PAL (“preferred” 5-HT₃-RA) and DEX for the prevention of both acute and delayed CINV in MEC [17]. Glioma CINV studies support this NCCN/MASCC/ASCO antiemetic guideline because neurokinin-1(NK-1)-receptor antagonists interact with standard glioma medications (e.g. dexamethasone; enzyme inducing antiepileptics) [18,7]. The high quality of evidence and low risk/benefit ratio support the NCCN/MASCC/ASCO guideline recommendation that PAL plus DEX be incorporated into MEC standard order-sets for malignant glioma patients. The NCCN guidelines further recommend assessing CINV risk factors (i.e., female, younger age, low alcohol use, and prior chemotherapy use) and state that a chemotherapy regimen’s emetogenic potential is the most significant predictor for CINV [19,20,4,17]. Chemotherapy can range in emetogenicity, with MEC and highly emetogenic agents causing CINV in > 30% and > 90%, respectively, of patients treated.

In the fall of 2011, a year’s review of computerized order-sets generated for patients receiving MEC at the PRTBTC revealed that antiemetic guidelines were followed only 41% of the time despite PAL availability. The major barrier to guideline adherence was knowledge, with 79% (11/14) of providers “lacking awareness” of the current antiemetic guidelines. However, education alone does not improve guideline adherence [21,22]. Studies evaluating strategies for implementing antiemetic guidelines concluded that standardized order-sets and audit-feedback improve the transferability and sustainability of guidelines into oncology practices [21,23,9]. Mertens et al found that only when adherence feedback was coupled with patient outcomes did non-adherence decrease significantly, from 73% to a sustained 0%, yielding reduced overall CINV [21]. Thus, a combination intervention with an audit-feedback strategy that translates evidence into practice was developed to improve the adherence of guideline antiemetic ordering for glioma patients treated with MEC.

PROJECT AIMS AND OUTCOMES

We proposed that the implementation of a combination intervention including (a) an education session, (b) risk-assessment tool with (c) computerized standard order-sets utilizing the 2012 NCCN/MASCC/ASCO antiemetic guideline would increase adherence to

antiemetic guidelines and ultimately improve the CINV CR rate and the QOL of malignant glioma patients. We pursued the following aims:

Primary Aim

To determine if the combination intervention would increase provider adherence to the NCCN/MASCC/ASCO antiemetic guideline for malignant glioma patients treated with MEC from the baseline adherence of 60% to 80%.

Primary outcome—The *adherence rate* was a ratio of the number of MEC orders with PAL/DEX to the total number of MEC orders. That proportion was determined by the aggregated data generated via the computerized ordering system queries.

Secondary Aim (1)

To determine if PAL/DEX can increase the acute and delayed CINV CR rate from 55% to 80% in malignant glioma patients receiving MEC.

CINV outcomes—*Acute complete response (CR)* is the proportion of patients achieving a CR during the first 24 hours following chemotherapy administration. *Delayed complete CR* is the proportion of patients achieving a CR during the delayed period (> 24-120 hours) following chemotherapy administration. Operational definitions of other secondary outcomes are as follows: (a) CINV CR: Absence of nausea/vomiting defined as no emetic episode or use of rescue medication; (b) CIV CR: Absence of vomiting episode or the use of vomit medication; (c) CIN CR: Absence of the use of medication to help nausea, or due to concern about the possibility of experiencing nausea. The CINV outcomes were captured via the Osoba survey.

Secondary Aim (2)

To determine if PAL/DEX will stabilize or improve QOL in malignant glioma patients within 24-120 hours of receiving MEC.

Quality of life (QOL) outcome in CINV—The QOL outcomes were measured via the valid and reliable instruments: Osoba (Cronbach's $\alpha=.85$), the Functional Assessment of Cancer Therapy-Brain (FACT-BR), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) surveys (Cronbach's $\alpha=.95$) [24,25][26,27,28]. The 10-item Osoba patient-reported survey addressed the impact of nausea and vomiting on daily functioning. The 50-item FACT-BR measured general QOL and glioma symptoms across five subscales [26,27]. The 13-item FACIT-fatigue has clinical meaningfulness if there is a ± 3.0 change in scores from baseline [28]. Surveys took 10-15 minutes to complete.

METHODS

Study Design

A single-arm, quasi-experimental study design was utilized to compare post-implementation adherence rates to baseline and historical control data to determine changes in the adherence and patient outcomes. This project involved the collection and review of de-identified

aggregated data, and thus the study was exempted by the Institutional Review Board at Duke University.

Setting

This project took place at the PRTBTC Adult Outpatient clinic, where six physicians and eight APPs order antiemetics via Duke's computerized ordering system. The majority of providers were female (64%, 9/14), with a median of 6.5 years of experience (range: 1-31). Half of the providers were trained in neurology, with the other half trained in oncology.

Sample

The innovation targeted the sample of order-sets chosen by the PRTBTC providers to measure guideline adherence. We reviewed all orders of the adult malignant glioma patients scheduled to receive *intravenous* MEC at Duke from September through November, 2012, to determine adherence to NCCN/MASCC/ASCO guidelines. The risk-assessment tool further divided MEC order-sets into three subsets, based on emetogenicity level within the MEC category: *low-level*: temozolomide (occurs < 1%); *medium-level*: irinotecan/bevacizumab, carboplatin/bevacizumab, temozolomide/irinotecan/bevacizumab; *high-level*: carboplatin/irinotecan/bevacizumab, methotrexate. As follow-up care, patients who received MEC were asked about their nausea and vomiting experience. Patients who completed surveys and received the guideline antiemetic order-sets became the sample for secondary analyses.

Study Procedures

A combination intervention consisting of (a) an educational provider training session, (b) a risk-assessment alert tool with (c) computerized standard chemotherapy order-sets containing the NCCN antiemetics regimen (PAL/DEX) with an audit-feedback strategy was implemented in the fall of 2012. Adherence data via computerized queries were collected by the nurse informaticist at baseline and monthly to account for any practice changes that occurred over time. The historical CINV CR rate was obtained from previous studies. Baseline data describing the current antiemetic practice for adherence, historical CINV CR, and baseline QOL data were used to compare and evaluate three post-intervention outcomes: (a) adherence to NCCN/MASCC/ASCO antiemetic MEC guidelines, (b) CINV CR rate, and (c) QOL. Outcomes were evaluated monthly over 3 months to assess adherence trends and to provide audit-feedback, ending by December, 2012.

Combination Intervention

On August 31, 2012, a 30-minute *educational session*, consisting of a PowerPoint presentation to update providers about the research supporting the new 2012 antiemetic guidelines and additional intervention components, was conducted. A copy of the antiemetic guidelines was given to all providers. At the time of ordering chemotherapy for adult patients with malignant glioma receiving MEC, a *risk-assessment tool* containing a check-off of the risk factors was provided [19]. The MEC risk factor then prompted the provider to choose the guideline antiemetic order-set. For IV regimens with moderately emetogenic potential, a *standardized order-set* containing the "preferred" antiemetics (PAL 0.25 mg IV

and DEX 10 mg IV) was available in the Duke computerized ordering system (Figure 1). Patients who receive a MEC regimen routinely are asked risk factors and CINV outcomes and to fill out FACT-BR surveys to report baseline CINV rate, and QOL. Repeat routine care assessments were conducted 24 and 120 hours post-chemotherapy to assess acute and delayed CINV CR rate and QOL, respectively. To promote awareness, adherence rates and patient outcomes were presented via monthly email/staff meetings.

Data Analysis

Descriptive statistics were used to summarize risk factors and emetogenicity level. The primary outcome, adherence to guideline orders, was evaluated historically (over 1 year) and at baseline (over a 3-month period) prior to project implementation. Post-intervention order-set adherence rates were then evaluated monthly for 3 months and overall. With 36 anticipated post-intervention *orders*, a one-sample binomial test comparing historical and post-intervention adherence rates was conducted at the 0.05 level of significance having 80% power to detect a difference between a 60% and 80% order-set adherence rate (STPLAN Version 4.5).

Secondary (*patient*) outcomes included (a) antiemetic efficacy and (b) QOL in patients receiving the recommended NCCN/MASCC/ASCO antiemetic during acute/delayed phases. Grunberg and Aapro have reported that a change in CINV rate of 10% is clinically meaningful [29]. With at least 22/36 patient order-sets projected to require PAL, a one-sample binomial test comparison of the observed CR rate with the historical benchmark of 55% had at least 80% power to detect an increase to 82.5%. Historical and prospective cohorts were compared to determine if CINV risk factors were distributed differentially between cohorts.

Means and standard errors were generated to describe FACT-BR/FACIT-fatigue/QOL pre- and post-intervention. For the FACT-BR/FACIT-fatigue, a linear mixed model that accounted for within-patient correlation assessed the relationship between time and outcome. Cronbach's alpha was computed for each subscore. A Wilcoxon signed rank test assessed whether QOL as measured by the Osoba subscales had changed from baseline.

RESULTS

Outcomes of this project were (a) the *adherence rates* to the antiemetic guideline order-sets, and (b) the *patient outcomes* (CINV CR rates; QOL) associated with receiving guideline antiemetics.

Adherence

Baseline adherence over 3 months was 58% (with a historical adherence of 41% over a one-year period). A total sample of 61 MEC *order-sets* was reviewed for monthly and overall adherence. Monthly adherence to the NCCN/MASCC/ASCO antiemetic guideline gradually increased from 58% to 88%, and, ultimately, to 92%, with a sustained and significant increase in the *overall* adherence rate to 90% (55/61; 95% CI: 80, 96; $P<0.05$), as demonstrated in Figure 2. Adherence at baseline and during monthly follow-up for all patients, as well as the subset of MEC regimens defined by emetogenicity level, is

summarized in Table 1. Within the MEC treatment group, adherence increased from 44% to 100% in *high-level* MEC regimens, whereas in *medium-level* MEC regimens, adherence increased from 77% to 84%. No patients received *low-level* intravenous temozolomide.

Patient Characteristics/Risk Factors

Risk factors for the 36 surveyed patients are shown in Table 2. Thirty-two (32) of those patients received the guideline antiemetic. The majority (95%) of patients who received guideline antiemetics had ≥ 3 risk factors, including prior CINV (75%) and low alcohol intake (100%).

Nausea and Vomiting

There was a significant and meaningful clinical increase in both the acute CINV CR rate of 75% (95% CI: 57, 89; $P < 0.05$), and the delayed CINV CR rate of 84% (95% CI: 67, 95; $P < 0.05$). The CINV, CIN, and CIV CR rates increased significantly and are presented in Table 3.

Quality of Life

For each of the FACT-BR/FACIT-fatigue subscales, Table 4 presents the mean score at baseline, and during the acute/delayed phases. There was no evidence of a statistically significant change over time in QOL. Cronbach's alpha ranged between 0.67 and 0.9 for these subscales. However, there was a meaningful clinical 3.0-point increase in fatigue, as defined by Cella, during the acute phase [28]. Osoba survey results showed no significant change in vomiting on the impact of daily function. There was a significant increase in nausea on the impact of daily function during the acute and delayed phases ($P = 0.001$, $P = 0.0005$, respectively). The median, third quartile, and maximum increase in nausea are 0, 0.4, and 1.6 for the acute phase, and 0, 0.5, and 1.8 for the delayed phase. This statistically significant change is not considered clinically significant given that only three patients had more than a 1-unit change in nausea score.

DISCUSSION

Multiple studies have demonstrated that providers mismanage CINV, but evidence-based methods to increase adherence to antiemetic guideline ordering and ultimately improve CINV are limited [30,3-5]. Our project showed that a combination intervention and audit-feedback strategy designed to translate evidence into an oncology practice significantly increased and sustained guideline adherence from 58% to 90%, while improving both acute and delayed CINV CR rates to 75% and 84%, respectively.

Implications for Practice

A survey by Grunberg et al [10] indicated that providers accurately predict acute vomiting but underestimate nausea and delayed CINV, since patients are often sent home without assessment of delayed CINV risk. Our combination intervention assessed and ameliorated both acute and delayed CINV. However, the lower CIN CR rates (acute 84%, delayed 88%) and higher CIV CR rates (acute 91%, delayed 97%) suggest that nausea was less controlled, and may not be a pre-symptom of vomiting or relieved by the same pre-antiemetic.

Furthermore, while patients reported nausea, they did not consistently use a rescue antiemetic, emphasizing that nausea measurement is subjective. These findings are supported by studies which suggest that nausea is associated with and should be managed with non-pharmacological and nutritional interventions [31,29]. Trial literature has combined the nausea and vomiting constructs into one dichotomous endpoint, but future designs should separate these two endpoints to better understand these different phenomena.

Burmeister et al. [30] demonstrated that guideline non-adherence is related to under- or overdosing of antiemetic, especially in the delayed setting. Tendes and colleagues [32] recommend that a CINV reduction score based on the actual antiemetic dose ordered may better evaluate guideline prescribing. We found that computerized standardized order-sets containing the accurate antiemetic dose and frequency are an effective method both to prevent guideline antiemetic under/overdosing and reduce acute/delayed CINV. This finding is supported by studies, emphasizing that computerized ordering can enhance adherence [33,34].

Risk-assessments demonstrated that 95% of our glioma patients were at a 60% risk for developing CINV, which alerted providers and may have influenced their antiemetic choice [35]. Yet, a regimen's emetogenic potential is the most significant predictor of CINV and may be the primary predictor of adherence [19,20,4,17]. Our combination intervention changed providers' antiemetic ordering practices, particularly for the patients receiving "high-emetogenicity level" MEC regimen, where adherence increased from 44% to 100%.

Informal diffusion of adherence (41% to 58%) occurred with increased awareness of antiemetic research prior to project implementation. The knowledge barrier relating to the current antiemetic guidelines was mitigated by an educational session. However, studies have shown that increasing knowledge alone will not transform practice. We agree with Burmeister, who stated that Mertens' [21] audit-feedback strategy of reporting adherence rates coupled with patient outcomes to antiemetic prescribers can drive change toward ordering antiemetic guidelines. We demonstrated that transformational and sustainable adherence practices can be achieved through this combination intervention and evidence-based audit-feedback strategy. Overall adherence increased to 90% (95% CI: 80, 96). To monitor and ensure sustainability, our nurse informaticist can periodically query the adherence rate of computerized order-sets, and the educational session can be re-implemented if future adherence falls below the limits of this confidence interval.

Limitations

While adherence improved significantly, thereby decreasing CINV, it is important to note that the analyses do not account for the lack of independence among orders (e.g., orders being from the same providers and patients). Additionally, the project focused on a glioma population, limiting generalizability to other cancers. We recognize another limitation is computerized ordering availability at other institutions. While pre/post intervention groups had similar CINV risks, use of historical control data to assess CINV rates in a non-randomized design is a limitation. Selection bias exists in secondary patient outcomes, as some patients who received the intervention did not fill out the CINV survey. This project was not powered to demonstrate QOL improvement but *suggested* that the appropriate

antiemetics did not decrease QOL. Further studies are needed to assess QOL associated with guideline adherence.

CONCLUSION

Well-designed, rigorous studies support the NCCN/MASCC/ASCO antiemetic guidelines for administering PAL/DEX before MEC to prevent CINV. A major limitation of promising glioma regimens is the associated high CINV rate due to the low concordance with the recent antiemetic guidelines. The combination of the educational session; risk-assessment tool; and computerized, evidence-based antiemetic order-sets was found to be an effective decision support intervention to increase antiemetic guideline adherence. Adding the strategy of monthly audit-feedback of adherence with patient outcomes increased and sustained guideline adherence. Our combination intervention and audit-feedback strategy allowed for successful adherence and translation of evidence into our oncology practices, which ultimately improved CINV in patients with gliomas.

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Appendices

Fig. 1.
Standardized computerized order-set with primary risk (emetogenicity level) assessment

Fig. 2.

Monthly adherence to antiemetic guideline:

¹ Adherence was 41% over a 1-year period 6 months prior to implementation;

² Adherence was 58% over a 3-month baseline period to match project period

Table 1

Adherence to NCCN Antiemetic Guidelines: Orders at baseline (62) and orders (61) post-intervention

MEC* Emetic Level	Baseline	Post-Intervention			
		September	October	November	Overall
Medium	20/26 (77%)	8/10 (80%)	12/14 (86%)	12/14 (86%)	32/38 (84%)
High	16/36 (44%)	6/6 (100%)	10/10 (100%)	7/7 (100%)	23/23 (100%)
Overall	36/62 (58%)	14/16 (88%)	22/24 (92%)	19/21 (91%)	55/61 (90%)

* MEC: Moderately-emetic chemotherapy

Table 2

Risk factors of 32 patients surveyed

Risk Factor	Received Antiemetic Guideline % (N=32)	Received Other 5-HT₃-RA Antiemetic %(N= 4)	Overall %(N=36)
Female	31(10)	75(3)	36(13)
Age < 50	19(6)	25(1)	19(7)
Motion sickness	6(2)	0(0)	2(6)
Pregnancy-related nausea /vomiting	0(0)	25(1)	1(3)
Prior CINV*	75(24)	75(3)	75(27)
Other nausea and vomiting	16(5)	25(1)	17(6)
Low alcohol (< 5 d/wk)	100(32)	100(4)	100(36)
Number of risk factors			
2	6(2)	0(0)	6(2)
3	63(20)	25(1)	58(21)
4	19(6)	50(2)	22(8)
5	13(4)	25(1)	14(5)
MEC Regimen Subsets (Emetic level)			
Medium	47(15)	100(4)	53(19)
High	53(17)	0(0)	47(17)

* CINV: Chemotherapy-induced nausea and vomiting

Table 3

Complete response (CR) rates among surveyed patients (32) who received antiemetic guideline

CR Rate [*]	Acute (N=32)	Delayed (N=32)
CIV [†]	29 (91%)	31 (97%)
CIN [‡]	27 (84%)	28 (88%)
CINV [§]	24 (75%)	27 (84%)

^{*} Historical data demonstrated a 55% CINV CR rate

[†] CIV CR: Absence of vomiting episode or the use of vomit medication

[‡] CIN CR: Absence of the use of medication to help nausea, or due to concern of the possibility of experiencing nausea

[§] CINV CR: Absence of nausea or vomiting defined as no emetic episode or use of rescue medication

Table 4
Quality of life summary from the surveyed patients (32) who received guideline antiemetic

Scale	Baseline			Acute Phase ^{//}			Delayed Phase ^{//}			Estimated Slope [†]	SE	P-Value
	N(*)	Mean	SE	Mean	SE	Mean	Mean	SE	Mean			
FACT-G [‡] : Physical (range 0-28)	30(2)	20.69	0.70	19.13	0.98	18.73	18.73	1.04	-0.31	0.25	0.21	
FACT-G: Social (range 0-28)	30(2)	24.76	0.56	24.32	0.65	24.44	24.44	0.66	-0.04	0.17	0.83	
FACT-G: Emotional (range 0-24)	29(3)	19.93	0.60	20.07	0.55	19.83	19.83	0.61	-0.03	0.16	0.84	
FACT-G: Functional (range 0-28)	30(2)	15.19	0.87	15.43	0.85	14.49	14.49	0.91	-0.17	0.23	0.48	
FACT-G: Total (range 0-108)	29(3)	80.67	1.77	78.98	2.02	77.49	77.49	2.54	-0.56	0.57	0.33	
Brain Cancer Subscale (range 0-76)	30(2)	51.20	1.77	49.78	2.00	49.17	49.17	1.96	-0.33	0.51	0.51	
FACT-BR [‡] : TOI (range 0-132)	30(2)	87.08	2.95	84.34	3.32	82.39	82.39	3.52	-0.81	0.87	0.36	
FACT-BR: Total (range 0-184)	29(3)	132.22	3.28	129.07	3.80	126.94	126.94	4.27	-0.91	1.01	0.37	
FACIT-fatigue[§] Scale (range 0-52)	30(2)	34.33	1.74	31.00	1.88	31.45	31.45	2.04	-0.38	0.51	0.46	

* missing

[†] From linear mixed model that assessed the relationship between time and outcome

[‡] FACT-G/BR: Functional Assessment of Cancer Therapy-General/Brain

[§] FACIT- fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue

^{//} Acute Phase: Period during the first 24 hours following chemotherapy administration

[¶] Delayed Phase: Period > 24-120 hours following chemotherapy administration