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SHORT COMMUNICATION

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Skipping day 2 antiemetic medications may improve chemotherapy induced delayed nausea and vomiting control: results of two pilot phase II trials

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Abstract *Background:* 5HT-3 antagonists and corticosteroids control less than 50% of delayed chemotherapy induced nausea and vomiting (CINV) episodes. *Materials and methods:* Two pilot phase II studies were conducted at our institution in which all patients received ondansetron 16 mg and dexamethasone 20 mg before highly and moderately emetogenic chemotherapy on day 1. Patients on study 1 received metoclopramide 10 mg PO q8 h, granisetron 0.5 mg PO QD and dexamethasone 8 mg QD on days 2 and 3, whereas only metoclopramide was continued on the same schedule on day 4. On study 2, patients received the same medications, but no drugs were given on day 2, and the same treatment schedule was given to them but from days 3 to 5 instead. Patients were interviewed on days 1 and 6. *Results:* Twenty-one patients participated on each study. There were no significant clinical differences between these two studied populations. Complete CINV control occurred from days 2 to 5 in 23.1% (95% CI: 8 to 47%) on study 1 vs 61.9% (95% CI: 38 to 81%) of the patients on study 2. By logistic regression, complete CINV control was correlated significantly with antiemetic treatment group (p=0.011) even when we considered only patients who achieved complete CINV control during the first 24 h (p=0.031). *Conclusions:* Skipping day 2 antiemetic medications does not seem to worsen delayed CINV control and may even improve it, perhaps by avoiding tachyphylaxis to these medications. A randomized controlled study is in progress to confirm these results.

Keywords Antiemetics · Granisetron administration and dosage · Economics · Vomiting · Chemically induced vomiting · Prevention and control of vomiting · Antineoplastic combined chemotherapy protocols · Tachyphylaxis

Introduction

Unfortunately, regimens containing 5HT3 receptor antagonists in association with corticosteroids control less than 50% of the episodes of delayed acute chemotherapy induced nausea and vomiting (CINV). 5HT3 receptor antagonists may have a low efficacy for delayed CINV control [1, 2]. It is possible that 5HT3 receptor antagonists given on successive days may induce tachyphylaxis [3] that could be responsible for their reduced efficacy. In fact, Sjoqvist et al. [4] showed that in rats, at the intestinal level, serotonin may accumulate in the presynaptic space after exposure to 5HT3 receptor antagonists and that inhibition of presynaptic serotonin uptake could circumvent tachyphylaxis to these medications [4]. In fact, corticosteroids, either alone or in combination with 5HT3 receptor antagonists, have comparable efficacy in this setting, suggesting that in contrast to their efficacy in acute control of CINV [1, 2]. The introduction in the clinic of the new neurokinin-1 receptor antagonist aprepitant represented an

important advance in the prevention of delayed CINV[5, 6] but its high cost precludes its wider use in our undeserved population of cancer patients.

To explore if tachyphylaxis to antiemeic medications, specially 5HT3 antagonists, would contribute to the poor results obtained in the control of delayed CINV with these medications, we conducted two pilot phase 2 studies at our institution. We tried to ascertain in these studies first if decreasing the dose of 5HT3 receptor antagonists (study 1) and then if delaying its introduction (study 2) could decrease tachyphylaxis and thus improve delayed CINV control. In the first study, we used a reduced dose of granisetron (0.5 mg PO), which we used in a previous study with good acute CINV control [7]. In the second study, we skipped day 2 administration of all antiemetic medications. We report in this paper the results of these two pilot studies.

Materials and methods

Our Institutional Ethics Committee approved these protocols. We included prospectively, after patients signed the informed consent forms, 42 chemotherapy naive cancer patients, 21 in each of these two protocols, who were older than 18 years of age and scheduled to receive moderately or highly emetogenic chemotherapy. We considered highly or moderately emetogenic chemotherapy regimens as those containing cisplatin, doxorubicin, or epirubicin at a dose higher or equal to 60, 50, and 50 mg/m^2 , respectively [8]. We excluded patients who had a serum creatinine or direct bilirubin two times higher than the upper limit of the normal level or a SGPT three times higher than the upper limit of the normal level. We also excluded patients who were pregnant, who reported vomiting or the use of antiemetics 24 h before the administration of chemotherapy, or who were also receiving radiation therapy. Patients with a history of brain metastasis or evidence of gastrointestinal obstruction were also excluded as were patients who used regularly corticosteroids or benzodiazepines before the initiation of chemotherapy.

All patients on both studies received ondansetron 16 mg and dexamethasone 20 mg before highly and moderately emetogenic chemotherapy on day 1 according to ASCO guidelines (PMID: 10561376). Patients on study 1 received metoclopramide 10 mg PO q8 h, granisetron 0.5 mg PO QD, and dexamethasone 8 mg QD on days 2 and 3, whereas only metoclopramide was continued on the same schedule on day 4. On study 2, patients received the same medications, but no drugs were given on day 2 and the same treatment schedule was given to them but from days 3 to 5. We defined vomiting as the elimination of gastric contents through the mouth and considered as two episodes if they occurred at least 1 min apart. We defined nausea as the sensation of imminent vomiting. For patients with more than one episode of nausea, we reported only the most severe one. Complete control of vomiting (CCV) and of both nausea and vomiting (CCNV) were defined as absence of any episode of vomiting and of both nausea and vomiting, respectively. Patients were reevaluated on day 6 when they brought a diary where they reported any emetic episodes experienced since chemotherapy administration until that time. They were also interviewed at this point for data accuracy and asked about side effects of the antiemetic medications received.

Quality of life (QOL) was evaluated through the Functional Living Index of Emesis (FLIE) [9], which consists of an 18-question survey assessing the effect of CINV on quality of life during the study period [11]. For this questionnaire, higher scores are indicative of a better control of CINV. Patients answered the FLIE questionnaire before study entry and on day 6.

We used the chi-square with Yates correction or Fisher exact tests to analyze discrete variables and ANOVA for continuous ones. We used the NCSS statistical package (Kaysville, Utah, USA; http://www.ncss.com).

Results

Table 1 shows the clinical characteristics and the types of chemotherapy administered to the patients from studies 1 and 2. Twenty-one patients participated on each study. There were no significant differences between these two study populations in terms of their clinical characteristics or of the emetogenicity of the chemotherapy they received. Table 2 shows the results for CINV control for both studies. Complete control of vomiting (CCV) occurred in 57% (95% CI: 34 to 78%) and in 80% (95% CI: 58 to 94%) of patients in studies 1 and 2, respectively. Complete CINV control (CCNV) occurred from days 2 to 5 in 23.1% (95% CI: 8 to 47%) on study 1 vs 61.9% (95% CI: 38 to 81%) of the patients on study 2. By logistic regression, CCNV was correlated significantly with antiemetic treatment group (p=0.011). To account for differences in acute CCNV control between studies, we restricted our analysis only to patients who achieved CCNV during the first 24 h; also in this subgroup we could observe by logistic regression that antiemetic treatment type remained significant for CCNV (p=0.031). On day 6, the FLIE score for study 2 patients was of 117,47±4.01 vs 106,76± 4.01 for group 1 (p=0.06). Table 3 shows the toxicities encountered in each of these two studies. We noted weakness, xerostomia, headache, and sleep disturbances as the most frequently encountered toxicities.

Discussion

Delayed CINV is difficult to prevent and its occurrence impacts adversely in the quality of life of cancer patients [10]. Unfortunately, despite encouraging results of 5HT3

Table 1 Clinical characteristics of the patients enrolled in studies 1 and 2

Patients characteristics	Study 1 Number(%) or mean ±SD(range)	Study 2 Number(%) or mean ±SD(range)
Sex		
female	18 (85,7%)	18 (85,7%)
male	3 (14,3%)	3 (14,3%)
Age	49,24±12,44 (18–67)	53,52±7,32 (42–69)
Weight(kg)	61,45±9,17 (44–78)	64,89±9,23 (49–83,6)
Alchool use		
Y	2 (9,5%)	2 (9,5%)
N	19 (90,5%)	19 (90,5%)
Site of primary tumor		
Breast	16 (76,2%)	16 (76,2%)
head/neck	3 (14,3%)	2 (9,5%)
lung		2 (9,5%)
Ovarian		1 (4,8%)
Bone	1 (4,8%)	
uerine cervix		
Emetogenic potential of the Chemotherapy		
High	4 (19%)	5 (23,8%)
Moderate	17 (80,9%)	16 (76,2%)

Table 3 Symptoms reported by patients during treatment

Symptom observed	Study 1 (Number)	Study 2 (Number)
Decreased apetite	7	11
Increased apetite	2	2
Diarrhea	1	3
Constipation	3	2
Headache	10	7
Xerostomia	12	9
Weakness	12	15
Rash	2	4
Fever	4	3
Sleepiness	8	11
Insomnia	10	7
Depression	2	4
Pruritus	1	0
Dry eyes	1	0
Edema	0	1
Dizzines	0	1
Epigastric pain	0	1
Increased urinary volume	0	2
Decreased urinary volume	2	3
Myalgia	0	1

receptor antagonists in acute CINV control, their efficacy for delayed CINV is questionable [1, 2]. In fact, the addition of these medications to dexamethasone has not significantly improved delayed CINV control [1]. One possibility to explain this disparity of efficacy of 5HT3 receptor antagonists in acute vs delayed CINV control may be tachyphylaxis. Repeated consecutive doses of these medications could lead to an increased accumulation of 5HT3 at the presynaptic level in the gastrointestinal tract [4] that could, in turn, decrease the activity of a next dose of a 5HT3 receptor antagonist. To clinically test this hypothesis, we devised two strategies tested through two pilot phase II trials at our institution to try to circumvent tachyphylaxis to these medications' effects: 1) decreasing the dose of 5HT3 receptor antagonist and 2) delaying its introduction (i.e., skipping 1 day of antiemetic medications).

We found that, surprisingly, patients who received no antiemetic medications on day 2 (study 2) apparently had superior complete control of their nausea and vomiting episodes than those who received these medications on day 2 (study 1). We believe that delaying antiemetic medications, including 5HT3 receptor antagonists, could,

Table 2 Results for CCNV (complete control of nausea and vomiting) and CCV (complete control of vomiting) for studies 1 and 2, for the first 24 hs (acute CINV control), from days 2 to 5 (delayed CINV control), and total control of CINV throughout the 6 days in which patients were evaluated

	24 hs Number (%)	Study 1 d2/d5 Number (%)	Total (d1/d6) Number (%)	24 hs Number (%)	Study 2 d2/d5 Number (%)	Total (d1/d6) Number (%)
CCV						
Yes	16 (76,19%)	12 (57,24%)	12 (57,14%)	17 (80,95%)	17 (80,95%)	17 (80,95%)
No	5 (23,81%)	9 (42,86%)	9 (42,86%)	4 (19,04%)	4 (19,04%)	4 (19,04%)
CCNV						
Yes	7 (33,33%)	5 (23,80%)	5 (23,81%)	13 (61,90%)	13 (61,90%)	13 (61,90%)
No	14 (66,66%)	16 (76,19%)	16 (76,19%)	8 (38,09%)	8 (38,09%)	8 (38,09%)

CCNV (complete control of nausea and vomiting) and CCV (complete control of vomiting) and CINV (Chemotherapy induced nausea and vomiting)

in fact, circumvent tachyphylaxis to these medications' effects. However, in the absence of a randomized trial, alternative explanations can be given for our results, such as a difference of acute CINV control between studies despite the use of the same acute CINV protocol. To account for acute CCNV differences, we also analyzed only patients who achieved acute CCNV and, even in this subgroup, antiemetic treatment type (i.e., delayed vs non-delayed introduction of antiemetics) were still significant for delayed CCNV. To our knowledge, no other studies exist that attempted to delay the introduction of antiemetic medication aiming at minimizing tachyphylaxis to these medications' effects.

This study has important limitations such a small sample size and a non-randomized design. Nevertheless, the encouraging preliminary results obtained in study 2 patients should lead to a confirmatory randomized study already in progress in which this hypothesis can be further tested.

We conclude that skipping antiemetic medications on day 2 after highly or moderately emetogenic chemotherapy is feasible and may even improve delayed CINV control. It is possible that circumventing tachyphylaxis to antiemetic medications, specially 5HT3 antagonists, may became a cheap alternative to improve delayed CINV control in the future.

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