Risk Model–Guided Antiemetic Prophylaxis vs Physician’s Choice in Patients Receiving Chemotherapy for Early-Stage Breast Cancer
A Randomized Clinical Trial

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IMPORTANCE Despite multiple patient-centered factors being associated with the risk of chemotherapy-induced nausea and vomiting (CINV), these factors are rarely considered when making antiemetic recommendations.

OBJECTIVE To compare risk model–guided (RMG) antiemetic prophylaxis with physician’s choice (PC) in patients receiving chemotherapy for early-stage breast cancer.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial of 324 patients with early-stage breast cancer undergoing chemotherapy (cyclophosphamide and an anthracycline) for the first time at 2 specialty cancer care centers in Ottawa from April 10, 2012, to September 2, 2014. Patients were randomized to either the RMG arm (n = 154) or the PC control arm (n = 170). Prior to each cycle of chemotherapy patients in the RMG group were categorized as low or high risk for CINV, and their antiemetic treatments were adjusted accordingly.

INTERVENTIONS Patients considered to be at low risk received standard dexamethasone and a 5-HT3 antagonist, while those at high risk also received aprepitant with or without olanzapine, based on their risk level. The PC control group received antiemetic agents according to the treating physician’s discretion.

MAIN OUTCOMES AND MEASURES The primary end points were control of both nausea and vomiting in the acute posttreatment period (first 24 hours after therapy) and in the delayed posttreatment period (days 2-5 after therapy).

RESULTS The total numbers of chemotherapy cycles delivered in the RMG and PC control groups were 497 and 551 respectively. In the acute period, significantly more patients in the RMG group reported no nausea (53.7% [95% CI, 49.2%-58.1%] vs 41.6% [95% CI, 37.4%-45.3%]; P < .001) and no vomiting (91.8% [95% CI, 89.0%-94.0%] vs 82.2% [95% CI, 78.8%-85.3%]; P < .001) compared with the PC control group. Similarly, significantly more patients in the RMG group reported no nausea (39.6% [95% CI, 35.3%-44.1%] vs 30.7% [95% CI, 26.8%-34.7%]; P = .01) and no vomiting (87.1% [95% CI, 83.8%-90.0%] vs 78.0% [95% CI, 74.3%-81.4%]; P < .001) in the delayed period respectively.

CONCLUSIONS AND RELEVANCE In this trial, the RMG antiemetic prophylaxis led to improved control of acute and delayed CINV compared with physician’s choice of therapy.

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Despite multiple variables being associated with the risk of chemotherapy-induced nausea and vomiting (CINV), patient-centered factors are rarely considered when making antiemetic recommendations. For patients receiving cyclophosphamide with anthracycline-based chemotherapy for early stage breast cancer, local, national, and international treatment guidelines recommend a serotonin receptor (5HT3) antagonist, dexamethasone, and a neurokinin-1 (NK-1) receptor antagonist based solely on the emetogenicity of the chemotherapy regimen.2,3

To help incorporate patient-centered factors into CINV prophylaxis, our research group previously developed and prospectively validated repeated-measures cycle-based models in patients with a broad range of malignant conditions to determine which patients were at high risk for acute (first 24 hours after therapy) and delayed (days 2-5 after therapy) CINV. Major predictors for acute and delayed CINV were consistent with the published literature and included younger age, receiving platinum- or anthracycline-based chemotherapy, and emesis in previous cycles as risk factors.4,5 The models were subsequently used to develop numerical scoring systems (indices) that are able to accurately identify patients at high risk for acute and delayed CINV prior to each cycle of chemotherapy (see eTable 1 in Supplement 1). These models have good predictive accuracy, and patients classified as high risk are 3 to 4 times more likely to develop acute as well as delayed CINV compared with patients deemed to be at low risk.6,7

Before any novel treatment approach such as risk model-guided (RMG) therapy is introduced into clinical practice, a randomized clinical trial is required to determine if it improves patient outcomes compared with usual care. To test the clinical utility of the risk models for preventing acute and delayed CINV, a randomized trial comparing RMG antiemetic therapy to a physician’s choice (PC) control group was conducted in patients receiving cyclophosphamide with anthracycline-based chemotherapy for early-stage breast cancer.

Methods

Patients with newly diagnosed stage I to III breast cancer and scheduled to receive chemotherapy with a cyclophosphamide- and anthracycline-containing regimen at either The Ottawa Hospital Cancer Centre or the Irving Greenberg Family Cancer Centre, Ottawa, Ontario, Canada, were approached about participating in the study, and written consent was obtained. Permission to conduct the study was received by the local institutional ethics review boards. The trial protocol is available in Supplement 2.

The most commonly used chemotherapy regimens were either 4 cycles (1 cycle every 2-3 weeks) of doxorubicin, 60 mg/m², and cyclophosphamide, 500 mg/m² (AC) or 3 cycles (1 cycle every 3 weeks) of fluorouracil, 500 mg/m², epirubicin, 100 mg/m², and cyclophosphamide, 500 mg/m² (FEC) as part of the FEC-docetaxel regimen.

At a Glance

- A randomized clinical trial comparing risk model-guided (RMG) antiemetic prophylaxis to a physician’s choice (PC) control group was conducted in patients receiving chemotherapy for early-stage breast cancer.
- In the acute period, significantly more patients in the RMG group reported no nausea (53.7% vs 41.6%; P < .001) and no vomiting (91.8% vs 82.2%; P < .001) compared with the control group.
- Significantly more patients in the RMG group reported no nausea (39.6% vs 30.7%; P = .01) and no vomiting (87.1% vs 78.0%; P < .001) in the delayed period, respectively.
- The RMG antiemetic prophylaxis led to improved control of acute and delayed chemotherapy-induced nausea and vomiting compared with PC therapy.

Study Design and Treatments

Eligible and consented patients were randomized (1 to 1) to the RMG group or to the PC control group (Figure 1). Patients randomized to the RMG group had their acute and delayed antiemetic risk scores calculated prior to each cycle of chemotherapy. Patients considered to be at low risk by the models (acute risk score <7 and/or a delayed score of ≤16) received antiemetic prophylaxis for a moderately emetogenic regimen based on local Provincial guidelines (antiemetic regimen level 0, see eTable 2 in Supplement 1). This consisted of dexamethasone and ondansetron (day 1, intravenous dexamethasone, 10 mg, and oral ondansetron, 8 mg, before chemotherapy; oral dexamethasone, 4 mg, and oral ondansetron, 8 mg, 8 hours later; days 2 and 3, oral dexamethasone, 4 mg twice daily, and oral ondansetron, 8 mg twice daily). Patients considered at high risk for CINV by the models (acute risk score ≥7 and/or a delayed score of >16) received antiemetic prophylaxis for a highly emetogenic regimen consisting of dexamethasone, ondansetron, and aprepitant as antiemetic regimen level 1 (see eTable 2 in Supplement 1) (day 1, intravenous dexamethasone, 12 mg, oral ondansetron, 8 mg, and oral aprepitant, 125 mg, before chemotherapy; and oral ondansetron, 8 mg, 8 hours later; days 2 and 3, oral aprepitant, 80 mg once daily, alone). If patients continued to be at high risk for CINV, then additional dexamethasone and olanzapine, 2.5 mg/d were added in subsequent cycles as antiemetic regimen levels 2 and 3 (see eTable 2 in Supplement 1). For patients randomized to the PC control group, the treating oncologist could choose any combination, dose, and duration of antiemetic therapy or she wished for each cycle of chemotherapy.

Study End Points and Data Collection

The 4 primary end points were complete control of nausea and vomiting in the acute and delayed periods after chemotherapy. Complete control was defined as the absence of either nausea or vomiting. Patients rated their control of both nausea and vomiting using a 4-point Likert scale. For nausea, both the nausea score (0 = none, 1 = able to eat, 2 = oral intake significantly decreased, 3 = requiring intravenous fluids) and severity (1 = none, 2 = mild, 3 = moderate, 4 = severe) were measured. Similarly for vomiting, both the vomiting score (0 = none, 1 = 1 episode in 24 hours, 2 = 2-5 episodes in 24 hours, 3 = 6 or
more episodes in 24 hours or need for intravenous fluids, 4 = requiring hospitalization) and severity (1 = none, 2 = mild, 2 = moderate, 4 = severe) were measured.

Secondary end points measured at day 5 after each chemotherapy cycle consisted of overall patient satisfaction with both nausea and vomiting control using a 4-point Likert scale (excellent, satisfactory, poor, or terrible) and quality of life (QOL). The QOL was assessed before the start of chemotherapy, at 24 hours, and at day 5 using the Functional Living Index-Emesis (FLIE) index, which is a validated questionnaire designed to measure the impact of CINV on a patient’s daily life. The FLIE index is composed of 2 domains, using 9 items for each domain with a 5-day recall. Each domain has a score ranging from 9 to 63, with higher scores indicating better control of CINV and improved QOL. Information on the use of rescue and nonprescribed antiemetics was also collected.

At study enrollment, data collection consisted of patient demographic and disease-related information, risk factors for CINV such as history of motion sickness, history of pregnancy-associated morning sickness, and daily alcohol consumption. Just before each cycle of chemotherapy, additional information was collected on the scheduled antiemetic prophylaxis, patient’s expectation to become nauseous following chemotherapy, food intake the morning of chemotherapy, number of hours slept the night before, and level of anxiety. Anxiety levels were measured using a 4-point Likert scale (graded as none, mild, moderate, and high). Patients were provided with a diary to record the number of episodes as well as the intensity and duration of nausea and vomiting during the first 24 hours and during days 2 to 5 following chemotherapy. This was supplemented with a telephone call by the study coordinator on days 1 and 5 after chemotherapy.

**Sample Size and Statistical Analysis**

The sample size calculation was based on our group’s earlier work in this area. We found that by the final cycle of chemotherapy, the proportion of patients experiencing at least 1 episode of acute emesis was 18% throughout all cycles of chemotherapy. One of the main objectives of the present study was to demonstrate that a patient-centered program using validated mathematical models can reduce the relative risk of acute emesis by 60%, which is equivalent to an absolute drop from 18.0% in the PC control group to 7.2% in the RMG group. At α = .05, 147 patients randomized into each group would provide an 80% power to detect a 60% relative reduction in the risk of acute emesis within the first 24 hours following chemotherapy. With the further assumption of a 10% patient dropout rate, 324 patients were enrolled into the current study.

Patient demographics and clinical and treatment characteristics were presented descriptively as means, medians, or proportions. Differences in the complete control of acute and delayed CINV over all cycles were compared using a main effects generalized estimating equations model, with an adjustment for clustering on the patient. Repeated-measures mixed models containing a “Group × Cycle” interaction were used to compare differences in QOL between groups over the first 5 days following chemotherapy over the full course of treatment. The mixed models contained the following variables: group; FLIE scores at baseline, 24 hours, and day 5; and cycle number. The data were analyzed based on the principle of intention to treat, and there were no adjustments for multiple comparisons on the rates of complete acute and delayed nausea and vomiting. Any missing values in the outcome variables were treated as missing at random and included in the analysis. All of the statistical analyses were performed using Stata, version 11.0 (Stata Corp LP).

**Results**

From April 2012 to November 2014, 324 patients were randomized into the RMG and PC control group (Table). Both groups were well balanced with respect to age, breast cancer


In the RMG group, 90% of patients received dexamethasone and a serotonin receptor antagonist as primary prophylaxis for the first cycle (Table). In the PC control group, 94.1% of patients received dexamethasone and a serotonin receptor antagonist as their primary prophylaxis. Only 4.1% of first cycles in the PC group contained an NK1 antagonist (aprepitant), and there were no patients receiving olanzapine (Table).

With subsequent cycles of chemotherapy, there were significantly more changes in antiemetic prescribing in the RMG group than in the PC group (see eFigure 1 in Supplement 1). In the RMG group, 90% of patients received aprepitant by the fourth cycle, and 40% had olanzapine added to cycles 3 and 4 (see eFigure 1 in Supplement 1). In contrast, in the PC control group, aprepitant was added to no more than 25% of cycles 2, 3, or 4.

Use of Rescue Medications and Nonprescription Antiemetics

Data on the use of prescribed rescue medication and associated interventions were also collected over the full course of chemotherapy in each of the 2 groups. Significantly fewer patients in the RMG group required prochlorperazine (37.0% [95% CI, 32.8%-41.4%] vs 46.2% [95% CI, 42.0%-50.5%]; P = .02) and methotrimeprazine (1.6% [95% CI, 0.7%-3.1%] vs 5.4% [95% CI, 3.7%-7.7%]; P = .001) for the control of protracted nausea and vomiting (see eTable 2 in Supplement 1). There were no statistically significant differences in the need for intravenous fluids, metoclopramide, and nonprescribed antiemetics.

Risk Model–Guided Antiemetic Use vs Physician’s Choice Model in Early Breast Cancer

Overall, 490 and 558 cycles of chemotherapy were completed in the RMG and PC control groups, respectively. The data also indicated good balance in predictive factors for CINV prior to each cycle over the full course of chemotherapy. Approximately 6% of patients in each group experienced anticipatory nausea before their chemotherapy, and there was a balanced distribution in the median number of hours of sleep the night before chemotherapy, the proportion who had a meal, and patient levels of anxiety (see eTable 3 in Supplement 1). Overall, 53.3% and 80.1% of patients in 497 cycles in the RMG group were categorized as being at high risk for acute and delayed CINV. This rate was comparable to the PC control group, with 59.0% and 78.6% of patients over 551 cycles considered by the models to be high risk for acute and delayed events (eTable 3 in Supplement 1).

Antiemetic Prescribing

Prior to the first cycle, 81.2% of patients in the RMG group were determined by the risk models to be at high risk prior to the first cycle. The study protocol required that the intravenous dexamethasone prechemotherapy dose be increased to 12 mg and that a neurokinin 1 (NK1) antagonist (aprepitant) be added for high-risk patients. Therefore, only 15.6% of patients in the RMG group received dexamethasone and a serotonin receptor antagonist as primary prophylaxis. Only 4.1% of first cycles in the PC group contained an NK1 antagonist (aprepitant), and there were no patients receiving olanzapine (Table).

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Control of Acute and Delayed CINV Across All Cycles of Chemotherapy

Complete control of acute nausea and vomiting was defined as the absence of either nausea or vomiting in the first 24 hours following chemotherapy across all cycles of chemotherapy. Significantly more patients in the RMG group reported no vomiting (91.8% [95% CI, 89.0%-94.0%] vs 82.2% [95% CI, 78.8%-85.3%]; P < .001) and no nausea (53.2% [95% CI, 49.2%-58.1%] vs 41.6% [95% CI, 37.4%-45.3%]; P < .001) relative to the PC control group (see eTable 4 in Supplement 1). Similar to the acute CINV results, significantly more patients in the RMG group reported no vomiting (87.1% [95% CI, 83.8%-90.0%] vs 78.0% [95% CI, 74.3%-81.4%];
Control of Acute and Delayed CINV by Cycle of Chemotherapy
A breakdown of the data by cycle of chemotherapy revealed consistently better CINV control over the first 24 hours (acute) and from days 2 to 5 (delayed) in the RMG antiemetic group (Figure 2). The prevalence of delayed nausea dropped from 70% after the first cycle to 30% by cycle 4 in the RMG group (Figure 2B). In contrast, the prevalence of nausea in the PC control group remained at 65% over the first 3 cycles of chemotherapy.

Patient Satisfaction With Overall CINV Control
Patient satisfaction with their overall nausea and vomiting control was also assessed after each cycle of chemotherapy. Over all cycles, 75.4% (95% CI, 71.4%-79.1%) of patients in the RMG group reported excellent control of their vomiting compared with 60.1% (95% CI, 55.8%-64.2%) in the PC control group (P < .01).

FLIE Index Scores
Patient QOL associated with CINV was assessed using the FLIE index. The improvement in nausea in the RMG group was reflected in the FLIE index scores, with significantly higher mean scores throughout the entire course of chemotherapy (P = .02; group × cycle interaction) (Figure 3A). The FLIE scores for vomiting control were consistently higher in the RMG group over the 4 cycles of treatment (Figure 3B), but did not reach statistical significance (P = .25; group × cycle interaction).

CINV Control in the RMG Group in Cycle 1
in High- vs Low-Risk Patients
In the RMG group, 81.2% of patients were categorized by the models as being at high risk for either acute or delayed CINV. Therefore, the protocol mandated the addition of aprepitant...
to the dexamethasone and 5HT3 receptor antagonist regimen. As a result, it could be argued that all patients with breast cancer receiving AC or FEC chemotherapy should receive triple antiemetic prophylaxis at cycle 1, and a risk model does not provide any additional information to guide therapy. To address this unknown, an exploratory analysis was undertaken within the RMG group to determine if there were differences in acute and delayed CINV control following cycle 1 between low- and high-risk patients, high-risk patients having received aprepitant (see eTable 1 in Supplement 1). The proportions of patients having complete control of acute and delayed CINV were numerically similar and not significantly different between low- and high-risk patients within the RMG group (data not shown).

Discussion

Despite important advances in its prevention, CINV remains among the most feared adverse effects of cancer chemotherapy.\textsuperscript{10,11} Poorly controlled CINV can result in reduced QOL, treatment delays, dose reductions, the need for additional antiemetic prophylaxis, increased health care resource use, and even premature discontinuation of chemotherapy. Despite the presence of multiple antiemetic guidelines,\textsuperscript{1,2} adherence is suboptimal,\textsuperscript{12,13} and nausea remains problematic in at least 50% of patients with cancer.\textsuperscript{14,15}

The limitations of traditional antiemetic trials are well recognized and include variability in the reporting of nausea and vomiting control, assessment only after a single chemotherapy cycle, inconsistent reporting of patient demographics, and the use of multiple chemotherapy and antiemetic regimens.\textsuperscript{16,17} It is not surprising that no optimal antiemetic regimen has yet been identified. What is more surprising is that despite patient risk factors for CINV being recognized in the clinic for many years, clinical trials or antiemetic guidelines have not incorporated these patient risk factors into their recommendations. Therapeutic recommendations in published guidelines are solely guided by the emetogenicity of the chemotherapy.

We have previously developed and prospectively validated acute and delayed CINV models to identify patients at highest risk.\textsuperscript{4,7} To test the clinical utility of the risk models, the present trial was performed to compare RMG antiemetic therapy with a PC control arm. The trial demonstrated that RMG antiemetic prophylaxis allowed for the better use of existing drugs in patients identified as being at high risk. Use of the RMG therapy led to the improved control of acute and delayed CINV over 3 to 4 cycles of AC or FEC chemotherapy relative to PC therapy. Significantly more patients in the RMG group reported excellent control of CINV over the course of care. Finally, the RMG use of antiemetics resulted in improved patient QOL-related nausea during their full course of chemotherapy. This finding is particularly relevant because nausea remains the real unaddressed issue in CINV.\textsuperscript{15,16}

The exploratory analysis within the RMG group also suggested that not all patients require aprepitant at cycle 1 following AC or FEC chemotherapy. Therefore, our risk models were able to accurately differentiate patients into low- and high-risk groups. In contrast to the approach of simply giving all patients aprepitant for all cycles of chemotherapy, this feature of the models ensures that patients at low risk are not overtreated. Given the economic benefits of appropriate prescribing, a pharmacoeconomic analysis is ongoing.

There are a number of study limitations. Given the nature of the intervention, the study could not be blinded, which could have introduced some selection bias. Despite the best efforts of the trial staff, CINV acute and delayed outcomes data were missing in 3% to 6% of patients. The study involved only 2 cancer centers within the same region of Canada, and therefore antiemetic use within the PC control arm may not be fully representative of Canadian or international prescribing patterns. The low compliance to American Society of Clinical Oncology (ASCO) antiemetic guidelines by physicians in the control group may have been due in part to confusion associated with the AC chemotherapy regimen. Earlier versions of the ASCO guidelines indicated that AC was moderately emetogenic, while in the most recent 2011 version, AC was reclassified as being highly emetogenic.\textsuperscript{2} Antiemetic guideline compliance continues to be challenging. Studies from the United States\textsuperscript{4,13} and Japan\textsuperscript{18} both showed low levels of compliance with local guidelines.

The study enrolled a homogenous sample of patients with breast cancer receiving either AC or FEC chemotherapy. Almost half of the patients in the trial were younger than 50 years; approximately 80% consumed less than 1 alcoholic beverage per day; and 50% to 55% had a history of morning sickness with pregnancy, all of which are factors that increase the risk of CINV. Given these risk factors, it was not surprising that between 60% and 80% of the patients in our study were categorized by the models as being at high risk for acute and delayed CINV. This led to significantly more patients in the RMG group receiving aprepitant and, subsequently, olanzapine over the course of their chemotherapy. However, the interpretation should not be that the models caused the overprescribing of antiemetics. Instead, the models led to appropriate, evidence-based antiemetic prescribing such as the protocol-mandated addition of effective agents. Notwithstanding all this, it would be interesting to test our risk models in less homogeneous disease contexts, such as lung and head and neck cancer.

Finally, the trial used simple 1 to 1 randomization and not a stratified block design. Therefore, due to chance alone, there were more patients (approximately 2.5%) randomized to the control arm of the study. However, as indicated in the distribution of patient and associated risk factors for CINV, overall balance was maintained between the 2 study groups, and there were no significant differences in patient variables between groups. Hence, the slightly higher number of patients in the PC control group had no bearing on the statistical analysis of the 4 primary end points.

Conclusions

In conclusion, vomiting and especially nausea continue to be a problem for many patients receiving chemotherapy. This study demonstrated that our CINV risk prediction models are...
easy to use in clinic and can lead to an improvement in CINV control and patient QOL. Future directions include the application of the CINV models to other disease types and their direct incorporation into chemotherapy ordering systems.

REFERENCES


