Effectiveness of Oral Antiemetics in an Ambulatory Setting

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ABSTRACT

Due to healthcare cutbacks, the Tom Baker Cancer Centre (TBCC) changed pre-chemotherapy antiemetic therapy from the IV to the oral route to contain costs. The objective of this study was to determine the effectiveness of the oral route for a range of emetogenic chemotherapy regimens.

Over a 2-month period, 64 patients undergoing 90 chemotherapy cycles were interviewed. Information on nausea, vomiting, daily activities, and diet for the three days following chemotherapy administration were recorded. Within the study-period, ondansetron, dexamethasone, and prochlorperazine were commonly prescribed to patients as pre-chemotherapy treatment. Over 80% of patient-cycles experienced no emesis in the first 24 hours. Good control of nausea and vomiting was reflected in the patients' ability to maintain their regular activity ($p=0.009$ for nausea and $p=0.00096$ for vomiting) and diet ($p=0.013$ for nausea, and $p=0.00005$ for vomiting). Seventy-eight percent of patients reported being counselled by a health professional and were aware that they were to take their oral antiemetic before the chemotherapy infusion.

From this practice setting study it can be concluded that the oral antiemetic regimens utilized at TBCC were very effective in the control of acute emesis afd patient care was not compromised by this route of administration.

Key Words: chemotherapy, effectiveness, oral antiemetics

RÉSUMÉ

Étant donné les compressions budgétaires dans le domaine de la santé, le Tom Baker Cancer Centre (TBCC) est passé du traitement antiémétique préchimiothérapie par voie intraveineuse au traitement antiémétique préchimiothérapie par voie orale, pour réduire ses dépenses. Le but de cette étude était de déterminer l'efficacité de ce traitement par voie orale pour toute une série de modalités chimiothérapeutiques émétogènes.

Sur une période de deux mois, 64 patients ayant reçu 90 séances de chimiothérapie ont fait l'objet d'une entrevue. Des renseignements sur les nausées, les vomissements, les activités quotidiennes et leur régime alimentaire au cours des trois jours suivant leur chimiothérapie ont été consignés. Durant la période de l'étude, l'ondansétron, la dexaméthasone et la prochlorpérazine ont été fréquemment prescrits aux patients avant leur chimiothérapie. Aucun vomissement n'a été rapporté au cours des premières 24 heures de la chimiothérapie, pour plus de 80 % des séances. Une bonne maîtrise des nausées et des vomissements a été obtenue, comme en a témoigné la capacité des patients à poursuivre leurs activités habituelles ($p=0,009$ pour les nausées et $p=0,00096$ pour les vomissements) et leur régime alimentaire ($p=0,013$ pour les nausées et $p=0,00005$ pour les vomissements). Soixante-dix-huit pour cent des patients ont mentionné qu'ils avaient reçu des conseils d'un professionnel de la santé et qu'ils savaient qu'ils devaient prendre leur antiémétique oral avant leur perfusion chimiothérapeutique.

Cette étude permet de conclure que les traitements antiémétiques oraux utilisés au TBCC étaient très efficaces pour maîtriser les épisodes émétogènes aigus et que la voie d'administration orale ne compromettait en rien les soins donnés aux patients.

Mots clés : antiémétiques oraux, chimiothérapie, efficacité

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INTRODUCTION

Chemotherapy-induced nausea and vomiting is a great concern for patients. Adequate control of these debilitating side-effects have received ongoing attention from researchers. As health professionals, our responsibility is to ensure that patients are getting the greatest benefit from antiemetics.

Prior to April 1, 1994, out-patients at the Tom Baker Cancer Centre (TBCC) were treated with antiemetics intravenously before receiving emetogenic antineoplastic agents. Due to healthcare cutbacks, Tom Baker Cancer Centre (TBCC) changed pre-chemotherapy antiemetic therapy from the IV to the oral route to contain costs. It was estimated that annual savings of $45,000 could be achieved though this change. Total savings were calculated by taking into consideration drug and operational

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costs. Operational costs included end-product testing on batched IV antiemetics, medical/surgical supplies, nursing and pharmacy time. Furthermore, oral antiemetics, which could be obtained in community pharmacies, had the potential to shift drug costs as well as operational costs from the Cancer Clinic, if effectiveness could be documented.

Oral efficacy was established from the literature.[1-4] Because this study was based in an actual clinical practice setting, there were no restrictions or attempts to standardize the chemotherapy protocols or antiemetic regimens prescribed. Physicians treated their patients based on diagnosis, progression of the tumour, response to chemotherapy, their clinical experience, and prescribed antiemetics, accordingly.

The 2-month evaluation took place 1 year after pre-chemotherapy antiemetics were changed from IV to oral. The objectives of the study were: 1) to determine the effectiveness of oral antiemetic regimens actually used in practice; 2) to determine patterns of patient counselling; and 3) to build recommendations for enhanced antiemetic control where problem areas were identified.

METHODS

Patient Selection

Patients undergoing chemotherapy were interviewed by one pharmacy student. Patients were eligible for the study only if they were receiving chemotherapy, planned to take their oral antiemetic prior to treatment, gave their verbal informed consent, and were not included in other clinical trials. Following each of their chemotherapy cycles, patients were asked to fill out a Symptom Diary Card (Glaxo - Feeling Your Best). Patients recorded their experience of nausea, vomiting, activity, diet and the antiemetic schedule actually used. Other data collected included the diagnosis, stage of the disease, treatment received, and current chemotherapy cycle number. The community pharmacy was contacted to verify the antiemetic(s) the patient was currently prescribed.

Chemotherapy Regimen Classification

Ranking the emetogenic potential of chemotherapy has been debated in the literature. For the purpose of this study, the ranking of chemotherapy protocols was achieved by equating the emetogenicity of the regimen to that of the most emetogenic agent in the combination using a previously published scale.[5] The protocols were subsequently placed into one of the four categories: high, moderate-high, moderate-low, and low (Table I). A survey of the medical oncologists on site confirmed this classification system.

Table I. Emetogenic Potential of Frequently Used Antineoplastic Agents

Emetogenic Potential	Drug
High (> 80%)	Chloroethyl Nitrosoureas Cisplatin (> 75mg) Cyclophosphamide (> 1g)
Moderate High (60-80%)	Cisplatin (< 75mg) Cyclophosphamide (< 1g) Procarbazine
Moderate Low (30-60%)	Carboplatin Doxorubicin Mitomycin C 5-Fluorouracil (> 1g)
Low (10-30%)	Bleomycin Etoposide Vinca Alkaloids

Adapted from Acronyms in Cancer Chemotherapy.[5]

During the data collection phase, patients were initially allocated to 1 of the 4 emetogenicity groups. However, since data collection did not aim at one disease state, chemotherapy protocol or antiemetic regimen, sample homogeneity became a fundamental problem. Upon recognition of this, only those patients receiving 1 to 6 cycles of chemotherapy, common chemotherapy protocols and antiemetic regimens were included in the analysis. However, as a result, the sample size in each of the 4 original emetogenic groups was too small for statistical analysis. Therefore, chemotherapy regimens were reclassified as high for the high and moderate-high groups, and low for the moderate-low and low groups. We believe this was valid as the clinical management of the patients in the collapsed groups, though different, was similar enough in many respects to warrant them being analyzed together.[6]

Statistical Analysis

The primary method of statistical analysis was the Chi-Square (X^2) test for categorical data. Contingency tables were utilized to analyze if two or more categorical variables were statistically independent. The results were interpreted using a two-tailed test with a cut-off for significance of 5%. The Fisher exact p-value was used for correction when the regular Chi-Square test was violated.

RESULTS

Patient Selection

During the period May 29 to July 28, 1995, contact was made with 161 patients, and 113 patients agreed to participate in the study to give a response rate of 70%. Some patients were excluded (as described above) in addition to those who received intravenous

pre-chemotherapy antiemetics alone or in combination with their oral drugs. As a result, 64 patients contributed 90 diaries on a cycle-to-cycle basis for analysis.

The basic demographic data and study exposure are illustrated in Table II. The population consisted of 52 females and 12 males with a mean age of 54 years. The most common diagnosis seen in the study for females was carcinoma of the breast and for males was lymphoma. CMF is a common treatment for breast cancer and CHOP is used to treat lymphoma.

Antiemetic Regimen

Ondansetron (OND)(37%) and dexamethasone (DEX)(29%) were the two most common drugs taken prior to chemotherapy infusion followed by prochlorperazine(PRO)(16%) (Table III). Combinations of DEX with metoclopramide(4%), OND(4%) and PRO(4%) were also observed. Other combinations made up the last 6%. On average, these antiemetic regimens were taken one-half hour before each treatment. A breakdown of the regimens prescribed for the high and low emetogenic groups revealed the antiemetics were prescribed according to the chemotherapy the patient was to receive (p=0.000004) (Table III). DEX and PRO were used most commonly for chemotherapeutic agents in the low group, and although OND was used in both groups, OND was given to patients receiving highly emetogenic chemotherapy in 60% of cycles. Because pre-treatment helps prevent chemotherapy-induced vomiting, we were interested in the response rate to these three (DEX, OND, and PRO) medications in the control of acute emesis as seen in Figure 1. Complete control was seen in all cycles with DEX. Ninety-two percent and 76% of OND cycles had complete control in the low and high groups, respectively. Lower numbers of cycles with no emesis were seen with PRO. The results seen in the low and high groups for OND, DEX, and PRO were not statistically different (Figure 1).

OND, DEX, and PRO were also commonly reported antiemetics for post treatment to prevent nausea and vomiting. These medications were taken when needed. It was determined from our review of the diary cards that patients tended not to take antiemetics on the second and third day post chemotherapy. Nine of 47 patients (19%) who did not take antiemetics in this phase did not take them if they were experiencing only nausea; whereas, only 2 patients did not medicate themselves if they vomited.

Table II. Patient Demographic Data and Chemotherapy Exposure for 90 cycles.

Site / Regimen	Chemotherapy Cycles	
Disease Site	Breast	54
	CNS	4
	Lymphoma	20
	Lung	5
	Other	7
Mean Number of Cycles		3
Chemotherapy Regimen *	CMF**	33
	CHOP	14
	3/4M	13
	EP	6
	Other	24

* CMF (cyclophosphamide, methotrexate, 5-fluorouracil), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), 3/4M (methotrexate, mitoxantrone, milomycin C), EP (etoposide, cisplatin)

** Although cyclophosphamide is a component of the CMF protocol, it is classically given orally on a multi-day, low dose schedule. It is not considered, by most medical oncologists, to be a highly emetogenic regimen.

Table III. Antiemetics Given Prior to Chemotherapy Cycles According to the Emetogenic Potential of each Regimen.

Antiemetic Given Prior to Treatment	Emetogenicity High	Low	Total Cycles
Dexamethasone	1	25	26
Dexamethasone/ Metoclopramide	2	2	4
Dexamethasone/Metoclopramide/Ondansetron	2	0	2
Dexamethasone/ Ondansetron	4	0	4
Dexamethasone/ Prochlorperazine	0	4	4
Dimenhydrinate	0	1	1
Metoclopramide/ Prochlorperazine	2	0	2
Ondansetron	21	12	33
Prochlorperazine	3	11	14
Total Cycles	35	55	90

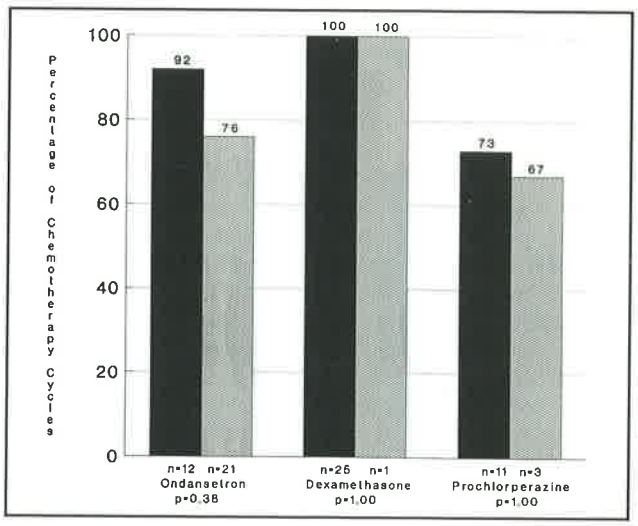

Figure 1. Response to single agent oral antiemetics by percentage of cycles with complete control of emesis. The hashed bars represent chemotherapy regimens which were judged to be highly emetogenic while the solid bars represent response to treatment of chemotherapy regimens with low emetogenic potential.

Complete Control of Nausea

Figure 2 illustrates the proportion of cycles in which nausea was not reported in the low and high emetogenic groups. There appeared to be a trend for a higher rate of control in the low group. Also, as the days progressed, improvement was seen in both groups. However, the results were not statistically significant. There was no relationship found between the antiemetic regimen taken and control of nausea.

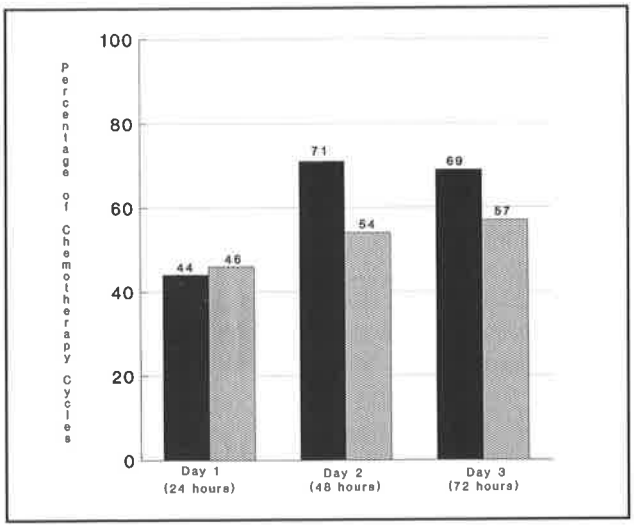

Figure 2. Percentage of chemotherapy cycles with complete control of nausea by number of days post chemotherapy. The hashed bars represent the 35 chemotherapy cycles which were judged to be highly emetogenic while the solid bars represent the 55 chemotherapy cycles with low emetogenic potential.

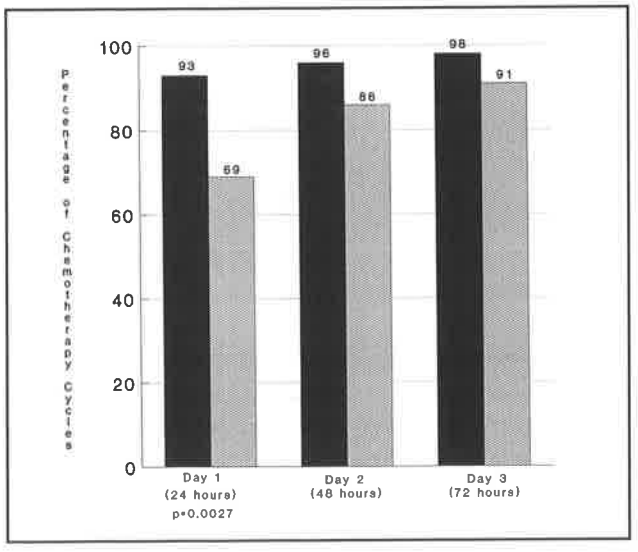

Figure 3. Percentage of cycles with complete control of vomiting according to the number of days post chemotherapy. The hashed bars represent the 35 chemotherapy cycles which were judged to be highly emetogenic while the solid bars represent the 55 chemotherapy cycles with low emetogenic potential.

Complete Control of Emesis

As expected, due to the lower emetogenic potential, fewer patients in the low group vomited (Figure 3), Patients in the low group vomited in less than 7% of the cycles within three days following chemotherapy. Overall, in 83% of cycles, patients had no acute (day 1) emesis, however, only on day 1 was there any apparent relationship between the emetogenic potential of the regimen and the control of this side-effect.

No relationship was observed between control of nausea/vomiting and sex, age, previous chemotherapy, chemotherapy cycle number, or diagnosis.

Activity and Diet

For cycles where patients reported no nausea on the first day, 68% of patients were able to maintain their regular activity and 90% were able to maintain their diet ($p=0.009$ and $p=0.013$, respectively). Similar results were seen on the next two days. The statistical results for control of vomiting and the ability to maintain regular activity (60%), and diet (87%) were significant only on day 1 ($p=0.00096$, $p=0.00005$, respectively).

Counselling

Patients recalled having a discussion about their medication with their nurse (46%), physician (16%), pharmacist (8%), or knew they had received written material (8%). However, 2% of patients could not remember being counselled and 20% (13/64) reported that they definitely had not received any counselling. This finding was better than the previous in-house survey conducted during the period June and July 1994, in which 32% (22/68) of patients reported that they were not counselled.

DISCUSSION

Ninety-three percent and 69% of cycles reported no emesis in the first 24 hours in the low and high emetogenic cohorts, respectively, to give an overall response rate of 83%. Therefore, it can be concluded that oral antiemetics, taken before infusion, were effective in over 80% of cycles seen in this study.

There was a lower response rate for nausea than vomiting control throughout the three days. This may suggest that nausea was a less understood side-effect, that the available antiemetics were ineffective or that the patients did not self-medicate post treatment. From our data, we observed that patients did not self-medicate if they were only experiencing nausea. There was a correlation between complete control of nausea/ vomiting and the ability to maintain regular activity/diet. Therefore, patients should be encouraged to continue with their medication so that nausea does not greatly impact their activities of daily living.

With the shift from IV to oral therapy it was important that patients were made aware of this change so that they were prepared before coming into the clinic. Counselling from their health professional was essential in communicating this fact so that patient care was not compromised. Seventy-eight percent of patients reported having been counselled and were aware that they had to take their medication before receiving their dose of chemotherapy.

The Alberta Cancer Board covered the cost of IV antiemetics before this project took effect. The cost of post-chemotherapy medication was the responsibility of the patient. The cost shifting to patients, as a result of the switch to oral antiemetics, has raised an ethical issue. The most commonly prescribed medications were OND, DEX, and PRO. The acquisition costs of DEX 4 mg and PRO 10 mg were not substantial (approximate cost: DEX 4 mg - $1.20 and PRO 10 mg $0.14, per tablet, respectively; North West Drug buying guide). However, the acquisition costs of OND 4 mg and 8 mg were approximately $12.00 and $18.00 per tablet, respectively, (North West Drug buying guide), and had a great impact on some patients. Most patients took the responsibility of absorbing the extra cost. However, for others who could not afford or forgot to bring their pre-dose medication with them to the clinic, pharmacy supplied medication to ensure that patient care was not compromised.

Evaluation of the three commonly prescribed antiemetics indicates that these drugs were appropriately prescribed for pre-treatment based on the emetogenic potential of the chemotherapy regimen, ($p=0.000004$). A closer examination of the response rates for complete control of acute emesis for OND, DEX, and PRO in each group showed that the rates were not dependent on the kind of medication taken. However, it was noteworthy to look at the individual cycles for patients who did not respond to their medication. A change to a different antiemetic or the addition of another medication may be required to enhance effectiveness of the regimen for those patients with one or more vomiting episodes in the acute phase.

The double-blind, crossover trial reported by Roila et al[7] has demonstrated that the combination of OND plus DEX is superior to OND alone (91% vs. 64% complete protection from vomiting) for patients receiving high doses of cisplatin >50mg/m^2. Another double-blind, comparative study with repeated low doses of cisplatin (20-40 mg/m^2) also reported that the OND plus DEX regimen was more efficacious than OND alone.[8] These 2 studies suggest that for the 8% of cycles in which vomiting was observed in the highly emetogenic chemotherapy group when only OND was administered, the addition of DEX may improve the outcome and may be the regimen of choice.

In a comparative, double-blind trial, OND plus DEX for patients receiving anthracycline and/or cyclophosphamide and/or etoposide, OND plus DEX were shown to have similar efficacy.[9] In our study, 12 patients in the low group received OND alone with very good control of vomiting in the first 24 hours. However, DEX alone also demonstrated excellent control of vomiting in patients receiving chemotherapy with a low emetogenic potential. Therefore, taking into consideration the high cost associated with OND, DEX may represent an equally efficacious, less expensive, alternative in these patients.

Markman et al demonstrated in a randomized, double-blind, crossover study that DEX was more efficacious than PRO for patients receiving CMF or doxorubicin either alone or in combination.[10] Replacement of PRO with DEX would produce better results for the patients who were not responding to PRO in the low group.

The results from this study provide an estimate of the actual response rate to antiemetic regimens used in practice. It should be noted that the chemotherapy protocols used at TBCC are likely typical of outpatient treatment. From this study it can be concluded that oral antiemetics were very effective in the complete control of acute vomiting in the majority of patients in this practice setting. However, the results from this study should not be compared directly to clinical trials because strict inclusion/exclusion criteria are often applied in clinical trials, whereas, few restrictions were utilized in this study.

Research into nausea/vomiting control and the impact it has on the patient's overall quality of life would have complemented this study. Although pre-dose antiemetic medications appear to have been appropriately prescribed and gave good response rates, a standardized antiemetic regimen that took into consideration the cost of the antiemetic, the emetogenic potential of the antineoplastic agents, the effectiveness of the medication, and the patient's overall quality of life would be very beneficial.

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