Retrospective Review of Antiemetic Medications Use in Patients Receiving Carboplatin Doses with an AUC ≥4

Katie Elsass, PharmD; Megan Kindred, PharmD, BCPS; Tamara McMath, MPH; Nirav Patil, MBBS, MPH

BACKGROUND: The 2017 National Comprehensive Cancer Network and American Society of Clinical Oncology antiemesis supportive care guidelines reclassified carboplatin doses with an area under the curve (AUC) ≥4 from moderate to high emetic risk. A high antiemetic regimen (defined as >90% frequency of emesis if not premedicated) requires the addition of a neurokinin-1 receptor antagonist or olanzapine.

OBJECTIVES: The primary objective was to determine if escalation of antiemetic drug from moderate emetic risk (>30%-90% frequency of emesis) to high risk was clinically necessary for patients who receive carboplatin doses with an AUC of ≥4. The secondary objectives were to evaluate the number of patients who received multiple chemotherapy agents, the primary cancer type, and associated costs with supplemental antiemetic agents.

METHODS: This retrospective chart review included patients who received at least 1 dose of carboplatin and had an AUC ≥4 at the OhioHealth Riverside Methodist Hospital or the Arthur G.H. Bing Cancer Infusion Center between June 1, 2015, and May 31, 2017.

RESULTS: Of 279 treatment plans provided during the study period, 11 (3.94%) patients required escalation from a moderate to a high antiemetic drug regimen, with a neurokinin-1 receptor antagonist or olanzapine. A total of 7 patients in the drug escalation population and 200 patients in the total study population had a primary gynecologic cancer (63.6% vs 73.3%, respectively; P = .492). The average wholesale price (AWP) for the cost of drug escalation, as well as any additional inpatient antiemetic doses was $675.10 per patient. The AWP for drug escalation alone was $663.80 per patient.

CONCLUSION: Within the study population, the majority of patients who received carboplatin doses who had an AUC ≥4 were successfully treated with a moderate antiemetic drug regimen. As a result of limited clinical findings, we could not find compelling evidence to change the emetogenic potential. These data raise questions about the current published antiemetic guideline recommendations from the National Comprehensive Cancer Network and the American Society of Clinical Oncology.

KEY WORDS: antiemesis guidelines, antiemetic chemotherapy, AUC ≥4, carboplatin, drug escalation costs, emetic risk, fosaprepitant, neurokinin-1 receptor antagonist, olanzapine

The National Comprehensive Cancer Network (NCCN) is comprised of 27 leading cancer centers in the United States that focus on creating patient and prescriber guidelines for the diagnosis of, treatment of, and supportive care for patients affected by cancer. Since 1995, the NCCN has aimed to aid oncology prescribers by providing evidence-based clinical recommendations. Although those guidelines often focus on treatment, they also provide a large amount of supportive care recommendations, including guidelines for antiemesis. The NCCN antiemesis guidelines are based on the following criteria—emetrisk of the chemotherapy agents administered, previous use of antiemetic medications, and the patient’s risk factors.1

The American Society of Clinical Oncology (ASCO) and the NCCN help to identify patients who are at an increased risk for chemotherapy-induced nausea and vomiting (CINV).1,2 Individuals who are at an increased risk for CINV include female patients, those aged <50 years, have morning sickness during pregnancy, have anxiety during daily activities, are prone to...
motion sickness, have a history of vomiting when sick, have a history of no or light alcohol use, and have previously received chemotherapy treatment.¹

The current NCCN’s antiemesis supportive care guidelines organize intravenous chemotherapy agents into 4 categories based on their emetogenic potential—high emetic risk (>90% frequency of emesis), moderate emetic risk (>30%-90%), low emetic risk (10%-30%), and minimal emetic risk (<10%).⁴ The medications that are often used and recommended for the treatment of CINV include a neurokinin-1 (NK₁) receptor antagonist, a 5-HT₃ receptor antagonist, dexamethasone, and olanzapine.¹²

Moderate and high emetic risk antiemetic agents include dexamethasone and 5-HT₃ receptor antagonists.² In addition, high emetic risk drug regimens are required to include an NK₁ receptor antagonist, olanzapine, or both.³ Antiemetic regimens with moderate emetic risk may include an NK₁ receptor antagonist or olanzapine, as needed, based on clinical judgment. Lorazepam may be used to reduce the risk for anticipatory nausea and vomiting.⁵ Other treatment options—such as promethazine, dronabinol, haloperidol, metoclopramide, scopomamine, prochlorperazine, and nabilone—can be used in patients who have received minimal emetic risk regimens or for the treatment of breakthrough CINV.¹

Since its approval by the US Food and Drug Administration in 1989, carboplatin has been classified as a moderately or highly emetogenic chemotherapy, depending on its area under the curve (AUC) dosing.¹ Landmark clinical trials were conducted by the National Cancer Institute of Canada and the Southwest Oncology Group and published in 1992 and 1993, respectively; their results led to the approval of carboplatin for the treatment of ovarian cancer.¹³⁴ These 2 clinical trials evaluated the rate of nausea and vomiting with carboplatin plus cyclophosphamide versus cisplatin with cyclophosphamide. These studies used a metoclopramide-based antiemetic drug regimen; the results showed less nausea and emesis in the carboplatin arm than in the cisplatin arm.¹³⁴ The dose of carboplatin was 300 mg/m² in these studies.¹³⁴ However, carboplatin dosing is frequently used in practice, and in an older study, it was calculated utilizing AUC and the Calvert formula, which incorporates renal function into dosing.⁵

The 2019 NCCN antiemesis guidelines now classify carboplatin doses with an AUC of ≥4 as high emetic risk and doses with an AUC of <4 as moderate emetic risk.¹ The NCCN guidelines cite multiple clinical trials to rationalize the escalation of carboplatin doses with an AUC of ≥4 from moderate emetic risk to high emetic risk.¹ In particular, 3 clinical trials evaluated patients who received an NK₁ receptor antagonist, dexamethasone, and a 5-HT₃ receptor antagonist versus dexamethasone and a 5-HT₃ receptor antagonist alone.⁶⁻⁸ These 3 studies evaluated multiple chemotherapy agents, including carboplatin. Each clinical trial showed statistical significance in the complete response of delayed (ie, >24-120 hours) CINV in patients who received an NK₁ receptor antagonist.⁶⁻⁸ One study conducted a subgroup analysis of carboplatin, which showed statistical significance in the complete response of delayed CINV (ie, 0-120 hours) for the overall phase with the use of the NK₁ receptor antagonist.⁶ Weinstein and colleagues demonstrated statistical significance in the complete response for the overall phase with fosaprepitant.⁸

Although these 3 studies demonstrated positive outcomes for the overall and delayed phases of CINV, they did not show any statistical difference in the acute phase.⁶⁻⁸ Furthermore, these studies are limited by the lack of information of the specific carboplatin doses evaluated, and by the use of single doses of the 5-HT₃ receptor antagonists, which are often also given on days 2 and 3 after chemotherapy and as-needed for the treatment of breakthrough CINV. The American Society of Clinical Oncology (ASCO) has also updated its antiemesis guidelines by recommending a 3-drug combination that includes an NK₁ receptor antagonist for patients who receive carboplatin with an AUC of ≥4.²

The objective of our study was to determine if it is necessary to use empirically a high emetic risk antiemetic drug regimen for patients who receive carboplatin doses with an AUC of ≥4 at a community teaching hospital that currently treats the majority of these patients with a moderate antiemetic drug regimen that includes a 5-HT₃ receptor antagonist and dexamethasone. It is necessary to evaluate the appropriateness of categorizing carboplatin doses with an AUC of ≥4 as high emetogenic potential for patient safety and for financial stewardship. The requirement of using an additional antiemetic medication in the regimen has a potentially unnecessary clinical burden on patients, as well as a financial impact on the health system. The addition of fosaprepitant poses the risk for additional side effects, as well as the potential risk for irritation on extravasation.⁹

A recent article has also highlighted a clinical shift toward the overuse of antiemetic medications. Encinosa and Davidoff estimated that the overuse of antiemetic medications may occur in approximately 24% of patients, with the highest rates among those who receive intravenous chemotherapy with high emetic risk.¹⁰ Pharmacists have the potential to have an impact on
the proper use of antiemetic drugs, and although the current literature suggests that pretreatment with an NK\(_1\) receptor antagonist may reduce the risk for delayed CINV that is associated with carboplatin, specific doses of carboplatin and patient characteristics have not been evaluated.

**Methods**

This retrospective, single-center chart review included patients with cancer aged ≥18 years who received at least 1 dose of carboplatin with an AUC of ≥4 between June 1, 2015, and May 31, 2017, and was approved by an Institutional Review Board. Patients were included if the carboplatin dose was administered at OhioHealth Riverside Methodist Hospital, a 1059-bed tertiary medical center or the Arthur G.H. Bing Cancer Infusion Center, a 20-chair outpatient infusion clinic connected to the hospital. Potential study participants were identified by clinical records and progress notes.

Patients were excluded if another high emetic risk chemotherapy was given concurrently with carboplatin, as classified by the NCCN guidelines. The list of high emetic risk intravenous chemotherapy agents is provided in Table 1. Patients were also excluded if they had complications when receiving the full dose of carboplatin, if they received carboplatin doses from an outside facility or provider, or if their enrollment in a clinical trial prohibited inclusion in a subsequent clinical trial. If an NK\(_1\) receptor antagonist or olanzapine was empirically started at the beginning of cycle 1 of the chemotherapy treatment plan, the patient was excluded from clinical evaluation, because of a lack of documented previous nonresponse to a moderate risk antiemetic regimen.

A total of 307 patients were screened for inclusion. All patients received carboplatin infusions during the designated time frame, and a total of 34 patients were excluded from the study. Therefore, a total of 273 patients were eligible for inclusion in the study and underwent chart review (Figure 1). Although 273 patients were included in the study, a total of 279 carboplatin treatment plans were included, because 6 patients had 2 carboplatin treatment plans in the electronic medical record. All eligible patients during the study time frame (from June 1, 2015, to May 31, 2017) are included in the analysis.

Demographic data were collected for all study participants and included age, sex, and primary cancer origin (gynecologic cancer vs other). Chart review was then performed to evaluate the primary and secondary outcomes.

The primary outcome was to identify escalation from a moderate to a high antiemetic regimen with the addition of an NK\(_1\) receptor antagonist and/or olanzapine to the chemotherapy treatment plan. The secondary outcomes included at least 1 other chemotherapy agent administered concurrently with carboplatin, primary cancer of origin, and the overall cost. The primary cancer origin in this study was gynecologic cancer, as a result of the gynecologic specialists who are located within the Arthur G.H. Bing Cancer Infusion Center, which therefore accounts for a large proportion of the patient population there.

### Table 1 Intravenous Chemotherapy Agents with High Emetic Risk

<table>
<thead>
<tr>
<th>Emetogenic Agent</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline and cyclophosphamide in combination</td>
<td></td>
</tr>
<tr>
<td>Carboplatin AUC ≥4</td>
<td></td>
</tr>
<tr>
<td>Carmustine ≥250 mg/m(^2)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide ≥1500 mg/m(^2)</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin ≥60 mg/m(^2)</td>
<td></td>
</tr>
<tr>
<td>Epirubicin ≥90 mg/m(^2)</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide ≥2 g/m(^2) per dose</td>
<td></td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td></td>
</tr>
<tr>
<td>Streptozocin</td>
<td></td>
</tr>
</tbody>
</table>

* ≥90% frequency of emesis.

AUC indicates area under the curve.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V1.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed February 28, 2019. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

* Figure 1 Study Patient Exclusion Criteria

- 307 patients received carboplatin infusions
- 22 received carboplatin doses with an AUC <4
- 3 patients receiving concurrent high emetic risk chemotherapy
- 1 patient received treatment outside of study site
- 7 patients started NK\(_1\) receptor antagonist with first cycle of carboplatin
- 1 clinical trial participant
- 273 total patients included in the study

AUC indicates area under the curve; NK\(_1\), neurokinin-1.
The overall cost of supplemental antiemetic agents resulting in drug escalation was calculated. The average cost per patient of the additional inpatient antiemetic agents used within the 7 days after carboplatin infusion was also calculated. The cost analysis was based on the average wholesale price (AWP) to represent the estimated cost.

Descriptive statistics comprised most of the statistical analysis in this study. Continuous variables are reported as means and standard deviations. Dichotomous and categorical variables are reported as frequencies with percentages. The comparison of frequency and percentages were performed using Fisher’s exact test. A P value of ≤ .05 was considered statistically significant.

Results

We identified 279 carboplatin treatment plans that met the criteria for inclusion. The study patient demographics, as well as the population who received drug escalation are shown in Table 2.

Of the 279 treatment plans, 11 (3.94%) unique patients required escalation from a moderate emetic risk antiemetic drug regimen to a high emetic risk antiemetic drug regimen. All patients were escalated to a high emetic risk antiemetic regimen with the addition of the NK1 receptor antagonist fosaprepitant to their subsequent treatment plans.

In addition, of the 273 patients in the study, 257 (94.1%) patients received at least 1 other non–high emetic risk chemotherapy agent along with carboplatin. Only 16 patients received carboplatin therapy alone. All 11 patients in the drug escalation population group received at least 1 other chemotherapy agent concurrently with carboplatin. There was no statistical difference in the proportion of patients who received multiple chemotherapy agents in the study population versus the patients in the escalation group (P = .999).

A total of 200 (73.3%) patients in the overall study population and 7 (63.6%) in the escalation group had a primary gynecologic cancer. There was no significant difference (P = .492) between the 2 groups. The individual patient’s gynecologic cancer origin is shown in Figure 2. In the escalation population, 3 patients had ovarian cancer, 3 patients had peritoneal cancer, and 1 patient had cervical cancer. Of these 11 patients, the most common (N = 5) chemotherapy agent used was paclitaxel (Table 3).

Cost was estimated by utilizing AWP for each antiemetic drug.11 The estimated cost for the antiemetic drug use in the escalation population consisted of the cost of escalation as well as as-needed inpatient antiemetic drug doses. The estimated cost of escalation and supplemental inpatient medication doses combined was $675.10 per patient at the time of the study. The AWP for drug escalation alone accounted for the majority of the cost at $663.80 per patient at the time of the study. The AWP for a single dose of fosaprepitant 150 mg at the time of the study was $384.11

Individual patients received multiple doses of fosaprepitant. This is reflected in the cost calculation and represents the total cost associated with escalation. The cost analysis was based on the average wholesale price (AWP) to represent the estimated cost.
most likely because of the potential side effects associated with fosaprepitant. Olanzapine was not used for escalation, as-needed antiemetic agents other than an NK₁ receptor antagonist or olanzapine within 7 days of their carboplatin infusion. The total estimated cost of inpatient supplemental antiemetic drug doses was approximately $31 per patient in the escalation group and $11 in the nonescalation group.

Discussion

Of the 279 treatment plans evaluated, only 3.94% of patients required escalation to a high antiemetic regimen with the addition of the NK₁ receptor antagonist fosaprepitant. Olanzapine was not used for escalation, most likely because of the potential side effects associated with atypical antipsychotics. The NCCN guidelines outline these side effects and discuss the risk for extrapyramidal symptoms, QT interval prolongation, dystonic reactions, and central nervous system depression.1

The number needed to treat in the specific study population to prevent 1 nonresponse to a moderate antiemetic drug regimen is 26 patients. Based on the number needed to treat and the AWP of fosaprepitant, this results in an approximate cost of $9984 to prevent 1 patient from nonresponse to treatment with a moderate risk antiemetic regimen. If each study participant received fosaprepitant for 1 cycle based on the current NCCN and ASCO guideline recommendations, the total estimated cost would equate to $107,136.

Approximately 1243 carboplatin infusions with an AUC of ≥4 were administered at Riverside Methodist Hospital and the Arthur G.H. Bing Cancer Infusion Center in the designated time frame, which would equate to an estimated total cost of $477,312 for the addition of fosaprepitant to the antiemetic regimen.

Although this study was unable to identify any significant patient risk factors associated with the drug escalation group, the majority of the patients in the escalation group received ≥1 chemotherapy agents concomitantly with carboplatin, and they were primarily female. However, this study was also unable to identify any significant risk factors, because of the overall characteristics of this patient population. Because of the gynecologic specialty available at the study site, the majority of the patients had a primary gynecologic cancer. Carboplatin has historically been a cornerstone option for the treatment of ovarian cancer, which may be another underlying cause of the majority of patients having a primary gynecologic cancer. Although these results apply to a specific population, the evaluated population (ie, mostly female) may inherently pose an increased risk for uncontrolled CINV.

The monitoring of inpatient supplemental antiemetic medication doses was used for patients who received chemotherapy in the inpatient setting, as well as for patients who received their dose in the outpatient setting and were then admitted to the hospital within the next 7 days. This practice was evaluated because of the inability to assess home use of antiemetic agents.

Of the 11 patients who required drug escalation, 4 patients still had uncontrolled CINV and required supplemental doses while in the inpatient setting. These patients might have had additional risk factors for CINV or underlying comorbidities that resulted in uncontrolled CINV even after the administration of an NK₁ receptor antagonist. These patients also had increased costs associated with the supplemental antiemetic drug use compared with the overall study population, which may indicate that they had an increased risk for CINV at baseline.

Limitations

As a result of its retrospective nature, this study has several notable limitations. We were not able to evaluate through manual chart review certain CINV risk factors, such as alcohol use, motion sickness, and morning sickness while pregnant. An assessment of all the potential risk factors could have helped to identify a patient population that would benefit from escalation to a high antiemetic drug regimen before initiating cycle 1 of chemotherapy.

We were also unable to collect data on patients’ home-based antiemetic drug use within this study. The excessive use of home-based antiemetic drugs, such as prochlorperazine, after chemotherapy also has the potential to be associated with side effects that may outweigh the clinical and cost benefits of omitting fosaprepitant treatment. Consequently, it is critical for pharmacists and providers to evaluate proactively the

### Table 3: Chemotherapy Agents Used, by Drug Escalation Population

<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Patients in the escalation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed, N</td>
<td>3</td>
</tr>
<tr>
<td>Paclitaxel, N</td>
<td>2</td>
</tr>
<tr>
<td>Paclitaxel + bevaxzumab, N</td>
<td>2</td>
</tr>
<tr>
<td>Paclitaxel + velparib + placebo, N</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin, N</td>
<td>1</td>
</tr>
<tr>
<td>Etoposide, N</td>
<td>1</td>
</tr>
<tr>
<td>Gemcitabine, N</td>
<td>1</td>
</tr>
</tbody>
</table>

Copyright © 2019 by Green Hill Healthcare Communications, LLC; protected by U.S. copyright law. Photocopying, storage, or transmission by magnetic or electronic means is strictly prohibited by law.
control of CINV by assessing all the risk factors and by observing required home-based antiemetic drug use. Although the use of AWP to assess cost does provide a benchmark for potential cost-savings, it does not account for group-purchasing cost reductions, as well as for many other factors that determine medication pricing. The pricing of fosaprepitant may also vary greatly, depending on the patient’s insurance coverage in addition to inpatient or outpatient designation of the infusion. An internal review of purchasing costs should be considered based on the practice site.

Finally, although this study spanned a total of 2 years, the study population was relatively small and was comprised of patients from a single practice site who had predominantly a primary gynecologic cancer. Expanding the study to review patients from all sites within the health system could have potentially helped to diversify the study population, which would strengthen the relevance of the clinical findings.

**Conclusion**

As a result of the limited clinical findings and the possibility of a substantial cost implication, the majority of patients who receive carboplatin doses with an AUC of ≥4 at this specific practice site can be pretreated empirically with a moderate emetic risk antiemetic drug regimen, without sacrificing quality of care. Escalation to a high emetic risk antiemetic regimen should be considered on a patient-specific basis, based on the clinical judgment of the provider. Patients should also be educated to alert their providers if CINV is not adequately controlled after each cycle of chemotherapy.

Treating patients who are receiving carboplatin doses with an AUC of ≥4 with a moderate antiemetic regimen has the potential to be clinically efficient, as well as provide a potential cost avoidance for the patient and the institution. Larger prospective trials are encouraged for the lateralization of these results among all health systems.

**Author Disclosure Statement**

Dr Elsass, Dr Kindred, Ms McMath, and Dr Patil have no conflicts of interest to report.

**References**