

# Use of Neurokinin-1 Receptor Antagonists in Patients Receiving Moderately or Highly Emetogenic Chemotherapy

**Miriam P. Rogers, EdD, APRN, AOCN®,  
and Linda Blackburn, MS, RN**

Chemotherapy-induced nausea and vomiting (CINV) is a serious adverse effect of chemotherapy that limits patients' physical, mental, and functional capabilities and may cause a delay or cessation of treatment. Antiemetic therapy can reduce the incidence of CINV. Research, using data from visits by patients receiving moderately (MEC) or highly emetogenic chemotherapy (HEC), identified that antiemetics were prescribed for 86% (in 2007) and 82% (in 2008) of patients receiving MEC or HEC. For these visits, 5-hydroxytryptamine-3 receptor antagonists were prescribed in at least 97% of visits for both years, whereas neurokinin-1 (NK-1) receptor antagonists were prescribed at a rate of 10% and 11%, respectively. Studies show that nurses and physicians underestimate the incidence of CINV after HEC and MEC. Oncology nurses often critically influence patients' selection of CINV therapy and can play a significant role in increasing awareness about the benefits of adding an NK-1 receptor antagonist to standard prophylactic regimens for acute and delayed CINV.

**M**ore than 70% of all patients with cancer who are receiving chemotherapy will experience nausea, vomiting, or both in the absence of any antiemetic (National Comprehensive Cancer Network [NCCN], 2009). In addition, 10%–44% will experience anticipatory nausea and vomiting (NCCN, 2009). Chemotherapy-induced nausea and vomiting (CINV) can have a significant negative impact on the quality of a patient's life (Ballatori et al., 2007; Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Cohen, de Moor, Eisenberg, Ming, & Hu, 2007; NCCN, 2009), perhaps leading to poor adherence to cancer treatment as well as physical, mental, and functional complications.

Despite advances in the management of CINV since the late 1980s, most patients continue to fear nausea and vomiting following chemotherapy (Bloechl-Daum et al., 2006; Carelle et al., 2002; Hoffman et al., 2004). Improvements in the management of acute CINV (in the first 24 hours after infusion) have resulted in lower incidences of nausea and vomiting at the site of care. However, when patients experience delayed CINV, they are generally not under the direct supervision of a healthcare provider. Because physicians and nurses do not witness patients' delayed CINV episodes firsthand, they often underestimate the scope of the issue (Grunberg & Ireland, 2005).

According to a survey conducted on site at the 33rd annual Oncology Nursing Society Congress in Philadelphia, PA, in May 2008, nurses reported that, aside from fatigue, CINV is the most

## At a Glance

- ◆ Nurses are critical to the prevention and management of chemotherapy-induced nausea and vomiting (CINV).
- ◆ Less than 12% of patients with cancer who would benefit the most from a neurokinin-1 receptor antagonist and 5-hydroxytryptamine-3 receptor antagonist combination antiemetic therapy actually receive it.
- ◆ Because quality of life and adherence to future chemotherapy regimens are significantly affected by CINV, all clinicians should recognize the value of effective antiemetic therapy as a factor in chemotherapy tolerability.

Miriam P. Rogers, EdD, APRN, AOCN®, is the director of oncology nursing at Greenville Hospital System in South Carolina; and Linda Blackburn, MS, RN, is a manager in clinical development at GlaxoSmithKline in Collegeville, PA. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society. (First submission July 2009. Revision submitted October 2009. Accepted for publication November 3, 2009.)

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**Table 1. Definitions for Emetogenic Potential Values**

POTENTIAL VALUE	RISK	FREQUENCY (%)
1	Minimal	Less than 10
2	Low	10–30
3	Moderate	31–60
4	Moderate	61–90
5	High	More than 90

Note. Based on information from Hesketh, 2008.

significant adverse effect of chemotherapy affecting quality of life for patients with cancer (Oncology Resource Center, 2009). In addition, nurses reported that 50% of their patients stopped or delayed chemotherapy because of CINV. Of the 581 nurses who responded to the 2008 survey, 70% reported that they approached the issue of CINV with a zero-tolerance policy, compared with only 40% of physicians who adopted the same policy.

The recognition of the neurokinin-1 (NK-1) receptor pathway in the development of CINV has led to a new class of antiemetics called NK-1 receptor antagonists (aprepitant was approved by the U.S. Food and Drug Administration in 2003). The addition of NK-1 receptor antagonists to standard therapy has been shown to be effective for the management of acute and delayed CINV (Jordan, Kasper, & Schmoll, 2005). The NCCN Clinical Practice Guidelines in Oncology™ and the American Society of Clinical Oncology guidelines recommend adding an NK-1 receptor antagonist to standard CINV-prevention regimens for patients receiving either moderately (MEC) or highly emetogenic chemotherapy (HEC) (Kris et al., 2006; NCCN, 2009). The NCCN panel specifically recommended that an NK-1 receptor antagonist be used for multiday chemotherapy regimens likely to be highly emetogenic and associated with significant risk for delayed nausea and vomiting (NCCN, 2009). Adoption of these guidelines, however, has been slow, and CINV remains an important target for improved therapeutic intervention (Grunberg et al., 2004; Jordan et al., 2005).

The purpose of this study was to examine the frequency of use of 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists and NK-1 receptor antagonists for the prevention of CINV.

## Methods

### Study Design and Patients

The analysis included data obtained from more than 29,000 patients and more than 200,000 chemotherapy visits for the 12-month period ending June 2007 and from more than 31,000 patients and more than 200,000 chemotherapy visits for the 12-month period ending April 2008. A patient visit was defined as any day on which chemotherapy was administered, provided the administration date was at least six days from the previous administration date (i.e., patients had only one visit in any seven-day period). The data reported included the projected number of annual chemotherapy patient visits in the United States during the specified time periods, stratified by level of emetogenic potential (Hesketh, 2008) (see Table 1), as well as the projected number of patient visits in which antiemetics were used. Results are reported for MEC and HEC regimens (emetogenic potential levels of 3, 4, or 5).

### IntrinsiQ Data Analysis

Analysis of the frequency of use of 5-HT<sub>3</sub> receptor antagonists and NK-1 receptor antagonists for the prevention of CINV was conducted by the IntrinsiQ data warehouse, using the company's IntelliDose® software to collect and process longitudinal chemotherapy records for patients with cancer. The IntrinsiQ data warehouse contains patient- and provider-level information for more than 160,000 patients with cancer and more than 12 million administrations of various drug therapies (IntrinsiQ, LLC, 2008). The data from IntelliDose are gathered from chemotherapy records of a representative population of more than 570 oncologists across the United States. The participating oncologists are representative of the overall population of oncologists in the United States with regard to specialty (67% medical, 20% hematologic, 9% gynecologic, and 4% pediatric), type of practice (64% office, 25% community hospital, 10% academic, and 1% Veterans Administration), size of practice, and geographic location.

IntrinsiQ's projection methodology is based on a cohort component approach that uses nationally available data to generate projection factors (IntrinsiQ, LLC, 2008). Data used in these calculations include IntelliDose census data, population data

**Table 2. Visits of Patients Receiving Therapy With 5-HT<sub>3</sub> and NK-1 Receptor Antagonists, June 2007<sup>a</sup>**

EP VALUE	VISITS FROM PATIENTS RECEIVING ANTIEMETIC TREATMENT					
	PATIENT VISITS	ANY ANTIEMETIC	ANY 5-HT <sub>3</sub> ANTAGONIST	ANY 5-HT <sub>3</sub> ANTAGONIST WITHOUT NK-1	ANY 5-HT <sub>3</sub> ANTAGONIST PLUS NK-1	NK-1 TREATMENT (%)
3	827,806	634,799	631,673	612,447	19,226	3
4	2,875,518	2,432,947	2,319,500	2,185,702	133,798	6
5	1,329,610	1,277,665	1,268,405	1,001,643	266,762	21
MEC plus HEC (EP 3–5)	5,032,934	4,345,411	4,219,578	3,799,792	419,786	10

<sup>a</sup> Values are projected annual patient visits based on samples of more than 29,000 patients and more than 200,000 chemotherapy visits collected during the 12-month period ending June 2007.

EP—emetogenic potential; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; HEC—highly emetogenic chemotherapy (EP 4–5); MEC—moderately emetogenic chemotherapy (EP 3); NK-1—neurokinin-1

**Table 3. Visits of Patients Receiving Therapy With 5-HT<sub>3</sub> and NK-1 Receptor Antagonists, April 2008<sup>a</sup>**

EP VALUE	VISITS FROM PATIENTS RECEIVING ANTIEMETIC TREATMENT					
	PATIENT VISITS	ANY ANTIEMETIC	ANY 5-HT <sub>3</sub> ANTAGONIST	ANY 5-HT <sub>3</sub> ANTAGONIST WITHOUT NK-1	ANY 5-HT <sub>3</sub> ANTAGONIST PLUS NK-1	VISITS RECEIVING NK-1 TREATMENT (%)
3	808,283	590,949	582,131	566,476	15,654	3
4	3,014,745	2,417,335	2,407,733	2,226,666	181,068	8
5	1,354,527	1,257,404	1,241,124	974,479	266,645	21
MEC plus HEC (EP 3–5)	5,177,555	4,265,688	4,230,988	3,767,621	463,367	11

<sup>a</sup> Values are projected annual patient visits based on samples of more than 31,000 patients and more than 200,000 chemotherapy visits collected during the 12-month period ending April 2008.

EP—emetogenic potential; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; HEC—highly emetogenic chemotherapy (EP 4–5); MEC—moderately emetogenic chemotherapy (EP 3); NK-1—neurokinin-1

(www.census.gov), oncologist distribution by state and specialty (American Medical Association, 2010), and cancer incidences by state (American Cancer Society, 2010). Datasets are updated monthly for the IntelliDose census data and yearly for the other components. However, the estimated use of antiemetic agents is based on projections. This is a limitation of the study.

## Results

The projected number of annual visits for patients receiving either MEC or HEC regimens for the 12-month period ending June 2007 was more than 5 million (see Table 2). Antiemetics were prescribed in a projected 86% of those visits. For the visits in which antiemetics were prescribed, 5-HT<sub>3</sub> receptor antagonists were prescribed at 97% of visits compared with NK-1 receptor antagonists at only 10% of visits. Results were similar for the 12-month period ending April 2008 (see Table 3). Antiemetics were prescribed in 82% of the projected 5.2 million patient visits. For the visits in which antiemetics were prescribed, 5-HT<sub>3</sub> receptor antagonists were prescribed at a projected 99% of visits compared with NK-1 receptor antagonists at a projected 11% of visits.

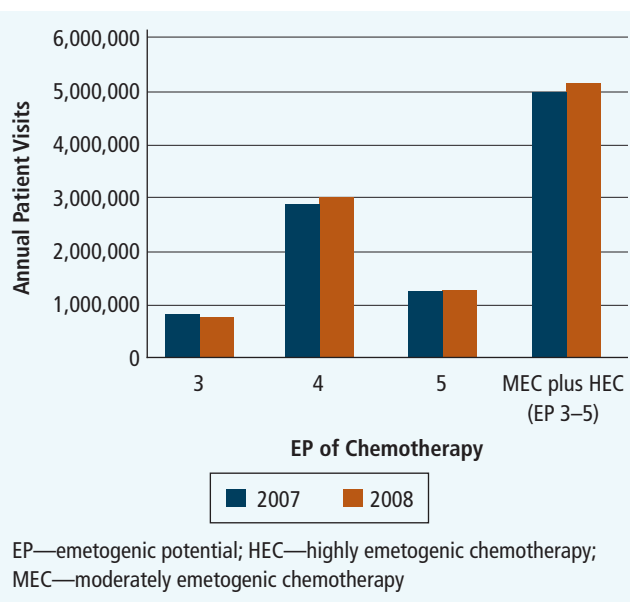
A comparison of the 2007 and 2008 data revealed similar numbers of annual chemotherapy patient visits (see Figure 1) for patients receiving MEC or HEC as well as a similar percentage of visits at which patients received 5-HT<sub>3</sub> receptor antagonists (see Figure 2). Relative use of NK-1 receptor antagonists remained low in both years, with little change in the percentage of penetration into the 5-HT<sub>3</sub> receptor antagonist market (see Figure 3).

## Discussion

The assessment and projections reported here illustrate the low use of NK-1 receptor antagonists in combination with 5-HT<sub>3</sub> receptor antagonists for the prevention of CINV in patients receiving MEC or HEC. Among patients who are the most eligible for antiemetic therapy (i.e., those receiving chemotherapeutic agents with emetogenic potential of 3–5), only 10% and 11% of patients in 2007 and 2008, respectively, received an NK-1 receptor antagonist in addition to a 5-HT<sub>3</sub> receptor antagonist.

Although this study includes data only from oncologists in the United States who used the IntelliDose software application, the data include information from a representative population of 570 oncologists, with even geographic distribution throughout the United States. In addition, the number of patients with cancer included in the IntrinsicQ data warehouse exceeds 160,000, with more than 12 million projected chemotherapy visits.

The addition of NK-1 receptor antagonists to standard therapy significantly improves emesis protection in both acute and delayed CINV by about 20% (Jordan et al., 2005). However, as evidenced by the results of this analysis, the addition of NK-1 receptor antagonists to standard antiemetic regimens has been slow. The low clinical use of NK-1 receptor antagonists despite their established antiemetic benefit (Grunberg et al., 2009; Jordan et al., 2009) and recommendations for their use in national guidelines (Kris et al., 2006; NCCN, 2009) may be linked to poor clinical understanding



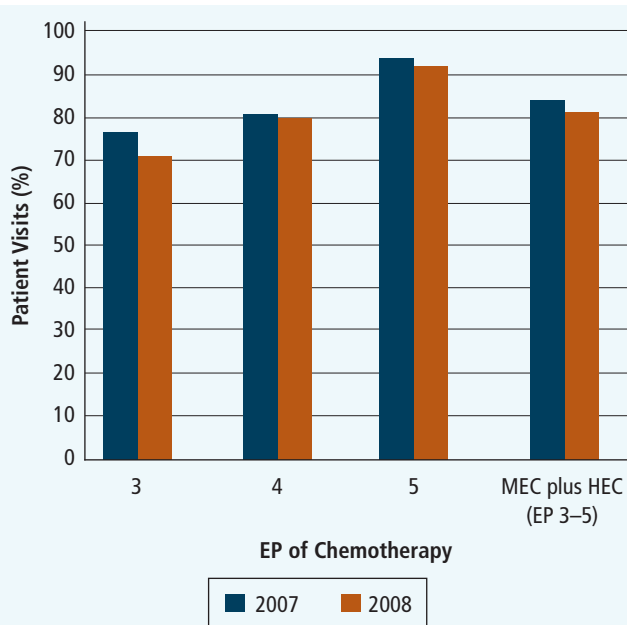
**Figure 1. Distribution of Annual Chemotherapy Patient Visits by Emetogenic Potential**

of the value of the addition of an NK-1 receptor antagonist to antiemetic regimens for patients receiving HEC or MEC.

The additional cost (which varies from region to region) associated with adding an NK-1 receptor antagonist to an antiemetic regimen also may contribute to low clinical use. Given the significant negative impact of CINV and the antiemetic protection provided in acute and delayed CINV, the benefits of adding an NK-1 receptor antagonist to the antiemetic regimen likely justify the additional cost. However, the authors acknowledge that the added cost associated with the addition of a second antiemetic agent is a potential barrier to prescribing and use.

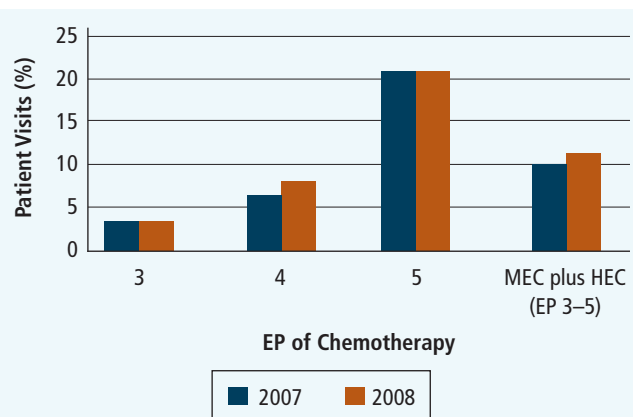
Potential drug-drug interactions should be considered when adding NK-1 receptor antagonists to CINV antiemetic regimens. NK-1 receptor antagonists can alter the metabolism of certain drugs and change their plasma concentrations; therefore, caution should be taken when used with any chemotherapeutic agent that is metabolized by CYP3A4 (including but not limited to docetaxel, paclitaxel, and etoposide). Also, NK-1 receptor antagonists have the potential to significantly reduce the clinical effectiveness of warfarin and oral contraceptives (NCCN, 2009).

Because quality of life and adherence to future chemotherapy regimens are significantly affected by CINV, clinicians should recognize the value of effective antiemetic therapy as a factor in chemotherapy tolerability. In a prospective, observational study of adult patients receiving MEC or HEC that compared rates of acute and delayed CINV with physician and nurse predictions, physicians and nurses accurately predicted the incidence of acute CINV but underestimated the incidence of delayed nausea and emesis after HEC by 21 and 28 percentage points, respectively, and delayed nausea after MEC by 28 percentage points. More than 75% of physicians and nurses underestimated the incidence of de-



EP—emetogenic potential; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; HEC—highly emetogenic chemotherapy; MEC—moderately emetogenic chemotherapy

**Figure 2. Percentage of Chemotherapy Patient Visits During Which Patients Received Antiemetic Therapy With 5-HT<sub>3</sub> Receptor Antagonists**



EP—emetogenic potential; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; HEC—highly emetogenic chemotherapy; MEC—moderately emetogenic chemotherapy; NK-1—neurokinin-1

Note. Percentages shown are for the number of visits at which patients received NK-1 inhibitors out of the total number of patients who were treated with 5-HT<sub>3</sub> antagonists.

**Figure 3. Penetration of NK-1 Therapy Into Chemotherapy Visits During Which Patients Received 5-HT<sub>3</sub> Receptor Antagonists**

layed CINV after HEC and MEC (Grunberg et al., 2004); therefore, a significant gap remains in healthcare professionals' awareness of the benefits of adding an NK-1 receptor antagonist to the standard prophylactic regimen for acute and delayed CINV.

Nurses are critical to the prevention and management of CINV and other aspects of supportive care. They directly encourage use and influence selection of CINV therapies, advocating for the most effective antiemetic regimens for their patients. To be more effective in this role of gatekeeper and advocate, oncology nurses should better understand current concepts in managing CINV to maximize effective antiemetic therapy. Additional assessment of factors influencing changes in clinical practice, such as the use of an NK-1 receptor antagonist in the management of CINV, should occur.

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**Author Contact:** Miriam P. Rogers, EdD, APRN, AOCN®, can be reached at mrogers@canursing.com, with copy to editor at CJONEditor@ons.org.

## References

- American Cancer Society. (2010). Surveillance, Epidemiology and End Results. Retrieved from <http://seer.cancer.gov/statistics>
- American Medical Association. (2010). DoctorFinder. Retrieved from <https://extapps.ama-assn.org/doctorfinder/home.jsp>

- Ballatori, E., Roila, F., Ruggeri, B., Betti, M., Sarti, S., Soru, G., . . . Deuson, R.R. (2007). The impact of chemotherapy-induced nausea and vomiting on health-related quality of life. *Supportive Care in Cancer, 15*, 179-185. doi: 10.1007/s00520-006-0109-7
- Bloechl-Daum, B., Deuson, R.R., Mavros, P., Hansen, M., & Herrstedt, J. (2006). Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *Journal of Clinical Oncology, 24*, 4472-4478. doi: 10.1200/JCO.2006.05.6382
- Carelle, N., Piotto, E., Bellanger, A., Germanaud, J., Thuillier, A., & Khayat, D. (2002). Changing patient perceptions of the side effects of cancer chemotherapy. *Cancer, 95*, 155-163. doi: 10.1002/cncr.10630
- Cohen, L., de Moor, C.A., Eisenberg, P., Ming, E.E., & Hu, H. (2007). Chemotherapy-induced nausea and vomiting: Incidence and impact on patient quality of life at community oncology settings. *Supportive Care in Cancer, 15*, 497-503. doi: 10.1007/s00520-006-0173-z
- Grunberg, S.M., Deuson, R.R., Mavros, P., Geling, O., Hansen, M., Cruciani, G., . . . Daugaard, G. (2004). Incidence of chemotherapy-induced nausea and emesis after modern antiemetics: Perception versus reality. *Cancer, 100*, 2261-2268. doi: 10.1002/cncr.20230
- Grunberg, S.M., Dugan, M., Muss, H., Wood, M., Burdette-Radoux, S., Weisberg, T., & Siebel, M. (2009). Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. *Supportive Care in Cancer, 17*, 589-594. doi: 10.1007/s00520-008-0535-9
- Grunberg, S.M., & Ireland, A. (2005). Epidemiology of chemotherapy-induced nausea and vomiting. *Advanced Studies in Nursing, 3*, 9-15.
- Hesketh, P.J. (2008). Chemotherapy-induced nausea and vomiting. *New England Journal of Medicine, 358*, 2482-2494. doi: 10.1056/NEJMra0706547
- Hoffman, M., Morrow, G.R., Roscoe, J.A., Hickok, J.T., Mustian, K.M., Moore, D.F., . . . Fitch, T.R. (2004). Cancer patients' expectations of experiencing treatment-related side effects: A University of Rochester Cancer Center-Community Clinical Oncology Program study of 938 patients from community practices. *Cancer, 101*, 851-857.
- IntrinsiQ, LLC. (2008). *IntrinsiQ research*. Waltham, MA: Author.
- Jordan, K., Kasper, C., & Schmoll, H. (2005). Chemotherapy-induced nausea and vomiting: Current and new standards in the antiemetic prophylaxis and treatment. *European Journal of Cancer, 41*, 199-205. doi: 10.1016/j.ejca.2004.09.026
- Jordan, K., Kinitz, I., Voigt, W., Behlendorf, T., Wolf, H.H., & Schmoll, H.J. (2009). Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. *European Journal of Cancer, 45*, 1184-1187. doi: 10.1016/j.ejca.2008.11.046
- Kris, M.G., Hesketh, P.J., Somerfield, M.R., Feyer, P., Clark-Snow, R., Koeller, J.M., . . . Grunberg, S.M. (2006). American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. *Journal of Clinical Oncology, 24*, 2932-2947. doi: 10.1200/JCO.2006.06.9591
- National Comprehensive Cancer Network. (2009). *NCCN Clinical Practice Guidelines in Oncology™ [v.4.0]: Antiemesis*. Retrieved from [http://www.nccn.org/professionals/physician\\_gls/PDF/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf)
- Oncology Resource Center. (2009). Breast cancer news. Retrieved from [http://patient.cancerconsultants.com/breast\\_cancer\\_news.aspx](http://patient.cancerconsultants.com/breast_cancer_news.aspx)