INVESTIGATING RACIAL DISPARITIES IN QUALITY OF CHEMOTHERAPY-INDUCED SIDE EFFECT MANAGEMENT AMONG MEDICARE BENEFICIARIES WITH EARLY-STAGE BREAST CANCER

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ABSTRACT

Devon Karnes Check: Investigating Racial Disparities in Quality of Chemotherapy-Induced Side Effect Management Among Medicare Beneficiaries with Early-Stage Breast Cancer
(Under the direction of Stacie Dusetzina)

If not controlled, chemotherapy-induced nausea and vomiting (CINV) can compromise quality of life (QOL) for patients with cancer and may lead to decreased chemotherapy adherence. Guidelines therefore recommend that patients receiving highly emetogenic chemotherapy regimens prophylactically use potent antiemetics (neurokinin-1 receptor antagonists, or NK1s) to prevent the side effect. Racial disparities in NK1 use may contribute to well-documented disparities in breast cancer patients' chemotherapy experience. We had three objectives: (1) Assess racial disparities in NK1 use; (2) Assess the role of NK1 use disparities in explaining racial variation in women's treatment experiences (namely, post-chemotherapy healthcare utilization); (3) Assess the impact of NK1 formulation changes on disparities over time.

Using 2006–2012 SEER-Medicare data, we identified a cohort of 1,130 early-stage breast cancer patients beginning highly emetogenic chemotherapy. We used Modified Poisson regression to assess relationships between 1) patient race and NK1 use, 2) patient race, NK1 use, and CINV-related healthcare utilization, and 3) chemotherapy initiation year and NK1 use. We examined any NK1 use and use of specific NK1 formulations (oral aprepitant and IV fosaprepitant). We present adjusted risk ratios (aRR) and 95% confidence intervals (CI).

Black women in our sample were 32% less likely than white women to use an NK1 (aRR: 0.68, 95% CI: 0.51-0.91) and 46% less likely to use aprepitant specifically (aRR: 0.54, 95% CI: 0.35-0.83). There were no disparities in fosaprepitant use. NK1 use disparities did not contribute to an increased incidence of CINV-related utilization among black women; risk of outpatient utilization was actually lower for black patients at 0.15, compared to 0.23 for white patients. All patients were more than twice as likely to use an NK1 in 2011 compared to 2007 (aRR white: 2.67, 95% CI: 2.13-3.35;

aRR black: 2.54, 95% CI: 1.03-6.25). However, racial gaps have persisted. In 2011, the likelihood of NK1 use was 0.64 for white patients, compared to 0.32 for black patients.

We observed persistent racial disparities in NK1 use. Disparities may be explained by patient-level access barriers or prescribing variation. Future research should assess the underlying causes of disparities and the impact of disparities on QOL and chemotherapy schedule adherence.

For my mom and dad.

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CHAPTER 1. OVERVIEW

Specific Aims

Patients beginning cancer treatment have consistently cited chemotherapy-induced nausea and vomiting (CINV) as a major and fearful concern.[1] Poorly controlled CINV can have severe physiological consequences, including dehydration, nutritional derangements, metabolic imbalances, and anorexia.[2] Inadequate CINV control can lead to deterioration of a patient's functional condition and quality of life (QOL). Further, hospital admissions, emergency department (ED) visits, and outpatient hospital visits after the first cycle of chemotherapy are both common and costly, with one study estimating the cost of treating CINV during the first cycle of chemotherapy at $5,299 among patients with a CINV-related visit, and $731 across all patients receiving moderately or highly emetogenic chemotherapy.[6] In addition to its implications for QOL and cost, uncontrolled CINV can lead to decreased chemotherapy adherence or even withdrawal from beneficial chemotherapy.[2, 7] CINV control is therefore a critical aspect of high-quality cancer care and has profound implications for patients' cancer care experience.

Oncology professional organizations produce and endorse clinical practice guidelines for the use of antiemetics to prevent CINV.[8–10] For several years, the guidelines have recommended prophylactic use of a neurokinin 1 receptor antagonist (an NK1), the newest and most potent class of antiemetic, in combination with other drugs for patients receiving chemotherapy with a high risk of CINV. Prior to 2008, aprepitant, an oral drug taken on days 1–3 of the chemotherapy cycle, was the only NK1 available. There are access and cost barriers to aprepitant use. First, many patients are required to fill a prescription for aprepitant at their home pharmacy. Second, aprepitant is expensive, and patients may be subject to high cost-sharing when filling the prescription. Another potential barrier is under-prescription of the drug, because providers' use of antiemetics has been shown to be suboptimal.[11–13] Evidence suggests that such barriers may disproportionately affect minority patients. Studies of patients with lung, prostate, and colorectal cancers have shown black race to be

negatively associated with use of antiemetic drugs.[14, 15] Whether this finding extends to NK1s and to other cancers is unknown. In addition, although research has demonstrated that black cancer patients may be more likely than white patients to have gaps in or to discontinue chemotherapy because of hospitalizations and acute illness,[16] possibly due to adverse effects of treatment, no study has assessed the role of CINV prophylaxis in explaining these disparities. Finally, analyses of recent data are needed to evaluate the impact of the availability of an intravenous NK1 (fosaprepitant) on disparities in NK1 use. Because fosaprepitant is administered in the clinic and reimbursed under different insurance provisions than oral prescription drugs (i.e., under medical rather than pharmacy benefits), its availability may help to obviate access and cost barriers related to use of oral therapy.

The long-term goal of this line of research is to narrow disparities in the quality of supportive cancer care. The objective of this study was to assess the existence and impact of racial disparities in prophylactic NK1 use among breast cancer patients, a population who frequently receives highly emetogenic chemotherapy. It was my central hypothesis that black women are less likely than white women to receive an NK1. Documenting black/white disparities in guideline-recommended CINV prophylaxis and whether and how disparities have changed over time is essential for informing interventions to address disparities in supportive breast cancer care. To that end, I pursued three specific aims using data from the SEER-Medicare linked database.

Aim 1: Assess the relationship between patient race and prophylactic NK1 use. *Hypothesis: Black women are less likely than white women to use an NK1.*

Aim 2: Assess the relationship between patient race and CINV-related healthcare utilization and, if disparities exist, assess the role of prophylactic NK1 use in explaining them. *Hypothesis 2a: Black women are more likely to have outpatient visits, emergency department visits, and inpatient admissions related to CINV following chemotherapy. Hypothesis 2b: NK1 use attenuates racial disparities in healthcare utilization.*

Aim 3: Assess longitudinal trends in use of fosaprepitant and the impact of fosaprepitant availability on racial disparities in prophylactic NK1 use. *Hypothesis 3a: Use of fosaprepitant has increased over time for both racial groups. Hypothesis 3b: Racial disparities in any*

NK1 use have narrowed due to the introduction of fosaprepitant, which may address cost and access barriers disproportionately affecting black patients.

This study elucidates racial disparities in NK1 use among women with breast cancer (Aim 1) and evaluates whether these disparities may help explain disparities in patient outcomes (Aim 2). It also assessed whether disparities in NK1 use are changing over time (Aim 3). The results help transition current cancer disparities research from focusing primarily on curative treatment to also considering supportive care and its implications for patients' cancer care experience. This work also has implications for policy, because it provides needed evidence about the effect of NK1 formulations and reimbursement sources on disparities in use.

Executive Summary

Patients beginning cancer treatment have consistently cited CINV as a major and fearful concern.[1] Poorly controlled CINV can have serious implications for patients' QOL,[2] healthcare services use and costs,[6] and adherence to potentially beneficial chemotherapy.[2, 7] CINV prophylaxis is therefore a critical aspect of high-quality cancer care and has profound implications for patients' cancer care experience.

Oncology professional organizations produce and endorse clinical practice guidelines for the use of antiemetics to prevent CINV.[8-10] The guidelines recommended prophylactic use of an NK1 in combination with other drugs for patients receiving chemotherapy with a high likelihood of CINV. Prior to 2008, aprepitant, an oral drug taken on days 1-3 of the chemotherapy cycle was the only NK1 available. Patients may encounter access and cost barriers to aprepitant use. Many patients are required to fill a prescription for aprepitant at their home pharmacy. In addition, aprepitant is expensive, and patients may be subject to high cost sharing when filling the prescription. Evidence suggests that such barriers may disproportionately affect minority patients. In fact, studies of patients with lung, colorectal, and prostate cancer have shown black race to be negatively associated with use of other, older antiemetic drugs. [14, 15] Whether this finding extends to NK1s and to other cancers is unknown. In addition, no study has assessed the role of disparities in CINV prophylaxis in explaining disparate outcomes by race. Finally, analyses of recent data are needed to evaluate the impact of the availability of an intravenous NK1 (fosaprepitant) on disparities in NK1 use. Because fosaprepitant is

administered in the clinic and reimbursed under different insurance provisions than oral prescription drugs, its availability may help to obviate access and cost barriers related to use of oral therapy.

This study contributes to the cancer disparities literature by assessing the existence and impact of racial disparities in prophylactic NK1 use among breast cancer patients, a population that frequently receives highly emetogenic chemotherapy. Specifically, this dissertation has three objectives, which correspond to three Specific Aims: 1) To assess the relationship between patient race and prophylactic NK1 use; 2) To assess the relationship between patient race and CINV-related healthcare utilization and, if disparities exist, assess the role of prophylactic NK1 use in explaining them; and 3) To assess longitudinal trends in use of fosaprepitant and the impact of fosaprepitant availability on racial disparities in prophylactic NK1 use.

To achieve these objectives, we used modified Poisson regression to assess the relationships between: 1) patient race and NK1 use, 2) patient race, NK1 use, and CINV-related healthcare utilization following chemotherapy, and 3) chemotherapy initiation year and NK1 use. We examined both any NK1 use and use of specific NK1 formulations (oral aprepitant and IV fosaprepitant). We present risks and adjusted risk ratios (aRR) with 95% confidence intervals (CI) for all outcomes.

In Aim 1, we found substantial racial disparities in NK1 use. Specifically, we observed that black women had a 32% decreased likelihood of using any NK1 for the prevention of CINV (aRR: 0.68, 95% CI: 0.51-0.91). When examining oral and intravenous NK1 formulations separately, black women had a 46% decreased likelihood of receiving oral aprepitant (aRR: 0.54, 95% CI: 0.35-0.83). We did not observe a statistically significant racial difference in women's receipt of IV fosaprepitant (aRR: 0.82, 95% CI: 0.51-1.33). The fact that we observed racial disparities in oral but not intravenous drug use supports the hypothesis that intravenous fosaprepitant may be more affordable and accessible for patients.

Two explanations for our observation of disparities in aprepitant use are that black women are: 1) equally as likely as white women to be prescribed aprepitant but less likely to fill their prescriptions, possibly due to financial or other access barriers; or 2) disproportionately likely to see providers who do not prescribe NK1s in accordance with clinical guidelines because they are more

likely to be treated in lower-performing settings.[15, 17] Both explanations seem plausible given our findings. Specifically, the fact that disparities in NK1 and aprepitant use were somewhat attenuated when factors related to socioeconomic status (SES) were added to the models suggests that the disparities are at least partly explained by SES differences between black and white women. These SES differences could translate into differential ability to pay for prescription drugs or differential access to high-quality care (including guideline-adherent antiemetic prescribing).[15, 17] Interestingly, geographic region also appeared to partly attenuate disparities, suggesting a potential role for geographic variation in prescribing in explaining disparities in NK1 use.

In Aim 2, we observed racial variation in CINV-related healthcare utilization in the 14 days following the first chemotherapy infusion. In unadjusted analysis, black women were 37% less likely than white women to have healthcare claims related to CINV. Estimates were consistent after adjustment for clinical variables but statistically non-significant (aRR: 0.66, 95% CI: 0.42-1.04). The racial difference in post-chemotherapy healthcare utilization did not extend to any use of healthcare services (aRR: 0.95, 95%CI: 0.89-1.03, p=0.21). NK1 use was positively associated with CINV-related utilization (aRR: 1.34, 95%CI: 1.07-1.68, p=0.01). This relationship persisted among white but not black women.

The direction of the racial difference in CINV-related utilization that we observed was unexpected. Whereas we hypothesized that, possibly due to underuse of NK1s, black women would experience more CINV-related utilization following chemotherapy than white women, in our sample, black women were actually less likely than white women to have healthcare claims related to CINV. It seems unlikely that racial differences in general care-seeking behavior explain this variation, given our lack of observation of racial differences in any services use in the 14 days after chemotherapy. Therefore, it may be that the variation we observed is specific to CINV or symptom management.

There are two main reasons black women may be less likely to have claims with diagnosis codes related to CINV. First, black and white women may be at equal risk of experiencing CINV but black women may be less likely to report this experience to their providers. Differential reporting could be the result of several factors. For example, different demographic groups may have differential thresholds for reporting symptoms to their providers.[18] Alternatively, others have suggested that

minorities may receive suboptimal care due to decreased self-efficacy, defined as patients' perceived ability in obtaining needed information and attention regarding their medical concerns.[19] A second potential explanation is that the black women in our sample may differ from white women with respect to unmeasured factors (e.g., body mass index), which could affect the incidence of treatment-induced side effects like CINV. [18, 20, 21] The positive association between prophylactic NK1 use and CINV-related utilization that we observed in Aim 2 was also surprising. We suspect that confounding by indication may account for this relationship. For example, patients' (or their providers') level of concern about CINV might help explain why patients who receive NK1s are also more likely to subsequently receive care related to the side effect.

Finally, in Aim 3, we hypothesized that fosaprepitant availability would lead to increased NK1 use for both black and white patients and that, by providing a more accessible and affordable alternative to three-day oral aprepitant, the introduction of fosaprepitant may have helped reduce racial disparities in NK1 use. Specifically, we hypothesized that in the post-approval period, providers may have prescribed fosaprepitant with increased frequency to patients who may experience cost or access barriers to prescription medication use, for example low income or minority patients.[22–24] In our sample, any NK1 and fosaprepitant use did in fact increase over time for both white and black patients. Patients of both racial groups were more than twice as likely to use an NK1 in 2011 compared to 2007 (aRR for white patients: 2.67, 95% CI: 2.13-3.35; aRR for black patients: 2.54, 95% CI: 1.03-6.25). Likewise, both groups experienced large increases in fosaprepitant use between 2009 and 2011 (aRR for white patients: 2.53, 95% CI: 1.75-3.65; aRR for black patient: 3.26, 95% CI: 0.67-15.91). However, racial gaps have persisted. In 2007, the likelihood of NK1 use was 0.24 for white patients and 0.13 for black patients, increasing to 0.64 and 0.32 for white and black patients, respectively, by 2011. That NK1 use has improved for all patients in our sample is encouraging and suggests that over time more patients are receiving adequate prevention of CINV. However, the persistent racial gap that we observed indicates that the CINV prevention needs of many black women are not being met. Thus, targeted efforts to increase NK1 use among black patients may be needed.

To inform these efforts, future research should assess the contribution of provider versus patient-level barriers to use. For example, black women may be more likely to receive care within lower-performing systems[17] where providers do not routinely prescribe NK1s in accordance with clinical guidelines[15] either because the systems' antiemetic order sets do not align with guidelines or because individual prescribers are unfamiliar with the guidelines.[11] Alternatively, black women and white women may be equally likely to be prescribed an NK1 but black women may be less likely to fill a prescription for aprepitant due to financial[22] or other access barriers[23, 24]. Strategies that facilitate providers' prescription of IV antiemetics, including fosaprepitant as a substitute for three-day oral aprepitant, may improve overall rates of guideline-concordant CINV prophylaxis, particularly for patients who have difficulty accessing or adhering to more complex oral regimens.

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CHAPTER 2. STUDY RATIONALE

Background

Racial Disparities in Breast Cancer Treatment and Outcomes

Racial disparities in breast cancer–specific mortality are well documented.[1] Biological differences may partially explain these disparities. Specifically, black women are more likely than white women to present with aggressive tumors (e.g., triple negative disease).[2] However, differences in tumor biology only partially explain racial disparities in patient outcomes, suggesting that access to and quality of care may contribute to these disparities.[1, 3–6] For example, black women are less likely to receive guideline-concordant mammographic screening for breast cancer prevention, resulting in a disproportionate burden of late-stage or terminal disease in this population.[7] Even when controlling for stage at diagnosis, however, black breast cancer patients fare worse than their white counterparts, possibly due to differential treatment.[8] Specifically, black women are less likely to receive radiation therapy[7] and adjuvant chemotherapy[3, 9] in accordance with clinical practice guidelines. Disparities also exist among women who do receive chemotherapy. Studies investigating racial and socioeconomic disparities in quality of systemic treatment have documented disparities in selection of chemotherapy regimens,[10] selection of chemotherapy doses in the initial course of chemotherapy,[11, 12] dose reductions in the course of chemotherapy,[13] prolonged time to chemotherapy completion,[14] and termination of chemotherapy before all planned cycles.[12]

Racial Disparities in Supportive Cancer Care

Racial disparities in breast cancer care are not limited to anti-neoplastic treatment. Several studies have documented disparities in supportive care, including symptom management, among patients with breast and other cancers. Specifically, racial/ethnic disparities have been demonstrated in outcomes related to symptom burden and severity,[15, 16] adequacy of pain treatment,[17–19] and patients' perceived unmet need for supportive services.[20] These disparities persist even as

supportive care is becoming recognized as an integral aspect of high-quality cancer care because of its implications for patient and caregiver quality of life (QOL). [21, 22] In breast cancer in particular, where advances in treatment have improved overall survival,[23] patients' QOL is an increasingly important endpoint of care.[24]

Racial Disparities in CINV Prevention (Aim 1)

Quality of CINV prophylaxis has received relatively little attention in the supportive breast cancer care literature, even though breast cancer patients routinely receive chemotherapy regimens that have a high risk of causing symptoms.[25] Although no studies have evaluated variation in quality of CINV prevention in the breast cancer setting, two have documented disparities in use of antiemetics among patients with other cancers. Only one study, conducted by Samuel and colleagues, specifically investigated racial disparities in the use of antiemetics for CINV prophylaxis as one of 20 cancer care quality indicators. [26] This study focused on patients with colorectal, prostate, and lung cancers. Although the study did document racial disparities in antiemetic use, the generalizability of the study's results is limited by its focus on the Veterans Affairs system. As well, the study used data from the early 2000s, before NK1s were available and recommended by clinical guidelines for the prevention of CINV. Another study conducted by Gomez and colleagues explored patterns of guideline-concordant antiemetic use among lung cancer patients.[27] Although the analysis was not focused on disparities, the authors did note racial and income disparities in antiemetic use. This study was also limited by its use of data from a single state's cancer registry and its lack of prescription drug data. In addition, because NK1 use was quite low in this sample (possibly due to the recent availability of aprepitant during the study period), NK1s were excluded from the analysis.

Whether documented disparities in guideline-concordant antiemetic utilization extend to breast cancer and NK1s is currently unknown. Research that assesses disparities in guideline-concordant antiemetic use among breast cancer patients will serve as a first step toward understanding the potential role of quality of CINV prophylaxis in contributing to racial disparities in breast cancer care and outcomes.

Racial Differences in Women's Treatment Experiences (Aim 2)

Assessing disparities in CINV control in the breast cancer setting is further justified by the existence of known disparities in women's treatment experiences. Previous research has demonstrated that black women are less likely than white women to adhere to guideline-recommended adjuvant chemotherapy regimens. Namely, they are more likely to experience dose reductions in the course of chemotherapy,[13] prolonged time to chemotherapy completion,[14] and termination of chemotherapy before all planned cycles.[12] As well, black women are more likely to experience delays during or termination of adjuvant chemotherapy due to acute illness, hospitalizations, missed appointments, and patient decision.[12] Although others have suggested that differential experience with chemotherapy could be due to racial differences in women's ability to afford the sometimes expensive medications needed to prevent and control side effects,[28] the role of side effect management in explaining disparities in women's treatment experience has never been empirically evaluated.

A handful of studies have examined patterns in women's healthcare utilization while undergoing adjuvant chemotherapy for early-stage breast cancer.[29–32] However, none included patient race as a covariate. A study by Enright and colleagues did include data on patients' income and found evidence of potential variation by income in patients' hospitalizations and use of the emergency department (ED) during chemotherapy, with lower income patients more likely than high-income patients to experience these outcomes.[33] Studies that assess racial disparities in side effect-related healthcare utilization and the link between quality of CINV prophylaxis and utilization will help clarify the potential role of side effect management in contributing to racial disparities in breast cancer patients' treatment experiences.

Changes in Drug Formulation and the Impact on Disparities in CINV Prevention (Aim 3)

NK1 formulation has changed over time, but how changes have impacted overall NK1 use and disparities in use has yet to be evaluated. Prior to 2008, aprepitant, an oral drug with a recommended three-day dosing regimen, was the only NK1 approved for CINV prophylaxis. Access and cost barriers to aprepitant use exist. First, in many cases, patients are required to fill a prescription for aprepitant at their home pharmacy rather than receive it in the clinic at the time of

their chemotherapy infusion. Second, the drug is expensive and patients may be subject to high cost-sharing, particularly under Medicare Part D. In a discrete choice experiment assessing patients' willingness to pay to prevent CINV, the authors concluded that cost contributed more to patients' choices about avoiding CINV than any other single attribute, suggesting that the cost of medications to prevent CINV may affect patients' likelihood of using of them.[34] In general, previous research supports a link between higher monthly medication costs and non-adherence [35, 36] and studies have suggested that cost-related barriers to use of and adherence to prescription medications for cancer and other conditions may disproportionately affect minority patients.[37–39]

In 2008, an intravenous, provider-administered formulation of aprepitant (fosaprepitant) was approved by the FDA, and in 2010, clinical trials demonstrated that a single-dose fosaprepitant infusion could serve as a full replacement for the three-day oral aprepitant regimen.[40, 41] Because fosaprepitant is administered once in the clinic, simplifying the dosing regimen and removing the requirement for patients to take an NK1 at home, it may decrease the number of patients receiving suboptimal CINV control.[42] As well, because it is covered under different insurance provisions, fosaprepitant may also be more affordable for patients. Research estimating the impact of fosaprepitant availability on overall use and disparities in use of NK1s could have implications for policies that drive providers' prescribing practices.

Study Rationale

Significance

This research advances our understanding of potential racial disparities in prophylactic NK1 use among Medicare beneficiaries receiving highly emetogenic adjuvant chemotherapy for breast cancer. It also assesses whether disparities in use are changing over time in response to the availability of alternative drug formulations and reimbursement. This contribution is significant because it provides actionable evidence to healthcare providers and policy makers attempting to reduce racial disparities in supportive breast cancer care.

CINV is a common and fearful side effect of chemotherapy that can have severe implications in terms of QOL, cost, and treatment adherence. CINV is a persistent problem for patients receiving chemotherapy[43] and can adversely impact their QOL.[44–46] CINV-related hospital admissions, ED

visits, and outpatient hospital visits are also costly.[47] In addition to its implications for QOL and cost, uncontrolled CINV can lead to decreased chemotherapy adherence and even early termination of beneficial chemotherapy.

Guidelines recommend the use of potent antiemetics, called NK1s, for patients receiving highly emetogenic chemotherapy. Prior to 2008, aprepitant, an oral drug, was the only NK1 available. Several factors may complicate its use. First, in most hospitals and private practices, providers cannot dispense aprepitant in clinic. Therefore, patients are usually required to obtain the drug from a pharmacy. Aprepitant is also very expensive and, particularly when reimbursed under Medicare Part D, patients may be responsible for a large portion of the cost. Evidence suggests that cost and access barriers to antiemetic use may disproportionately affect minority patients [26, 27]. Understanding the relationship between race and NK1 use among breast cancer patients is important because this population frequently receives highly emetogenic chemotherapy. As well, research has demonstrated that black breast cancer patients may be more likely than white patients to have gaps in or to discontinue chemotherapy because of hospitalizations and acute illness,[12] possibly due to adverse effects of treatment. No study has yet assessed the role of CINV control through use of antiemetics in explaining these disparities.

Changes in NK1 formulation and reimbursement may have narrowed disparities in use. In 2008, the FDA approved the intravenous fosaprepitant for use as a substitution for day 1 of the three-day oral drug. In 2010, the FDA approved a new dosage of fosaprepitant that would replace all three days of the oral drug. Subsequently, clinical guidelines changed to recommend the use of either oral aprepitant or single-dose fosaprepitant. Analysis of recent data is needed to evaluate the impact of the availability and recommendation for use of fosaprepitant on disparities in use of NK1s. Because fosaprepitant is administered in the clinic as a single dose, removing the requirement for patients to fill and take the medication prior to and after their chemotherapy infusion, it is expected to decrease the number of patients receiving suboptimal CINV control.[41] In addition, because it is covered under Medicare Part B, fosaprepitant may also be more affordable for patients. Although Part B tends to have 20% co-insurance for all services, most Medicare beneficiaries have supplemental insurance coverage to assist with their out-of-pocket Part B costs.[48]

This study examines potential racial disparities in high-quality CINV control in ways that have important implications for clinical practice and policy. The results of this study will inform future research, clinical practice, and policy. Specifically, future research can be undertaken to elucidate the source(s) of disparities (cost, access, and under-prescribing) and, thus, potential interventions to address them. Identifying a link between NK1 use and CINV-related healthcare utilization is valuable in and of itself for informing interventions to improve the cancer care experience and outcomes for all patients in the setting of breast and possibly other cancers. Finally, understanding how formulation and reimbursement changes have affected NK1 use may inform policies and interventions to facilitate prescription and use of IV antiemetics.

Innovation

Research on breast cancer disparities has focused predominantly on describing disparities in curative treatment, particularly adjuvant systemic treatment. Numerous studies have documented that African American women are more likely than white women to underuse adjuvant chemotherapy,[49] and that, among patients who do initiate adjuvant chemotherapy, disparities exist in the selection of chemotherapy doses in the initial course of chemotherapy,[11, 12] dose reductions in the course of chemotherapy,[13] prolonged time to chemotherapy completion,[14] and termination of chemotherapy before all planned cycles.[12] Potential disparities in the quality of cancer treatment–induced side effect management, however, remain largely unstudied.

Without a better understanding of patterns and potential disparities in side effect management and how changes in the availability and reimbursement of supportive medications have impacted these patterns, the field cannot advance toward developing strategies to improve the cancer care experience and outcomes of breast and other cancer patients. This research is innovative mainly because it represents a substantive departure from the status quo by shifting the focus of breast cancer disparities research from describing the existence of disparities in curative treatment to investigating potential disparities in side effect management, which may impact patients' QOL as well as the quality of their treatment and outcomes.

This study assesses the relationship between patient race and the use of recommended antiemetics (NK1s) for the prevention of CINV among women receiving highly emetogenic adjuvant

chemotherapy for breast cancer. It also assesses the role of NK1 use in explaining potential racial disparities in patient outcomes, including ED visits and hospitalizations. Although others have speculated that disparities in breast cancer treatment and outcomes may be due, in part, to black women's underuse of prescription medications to control adverse effects of treatment,[28] racial disparities in the use of these medications and their impact on outcomes have not been studied. Findings from this study can provide an example of new research focused on assessing potential disparities in the quality of supportive cancer care and the impact of these disparities on patient outcomes.

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CHAPTER 3. METHODS

Conceptual Model

Analyses followed a conceptual model adapted from Andersen's behavioral model of healthcare services use. As described in Figure 1, the model demonstrates how environmental factors and population characteristics (including predisposing characteristics, enabling resources, and need) influence healthcare utilization behaviors and, ultimately, health outcomes.[1]

Predisposing Characteristics

There are several indirect pathways through which patient race may impact utilization of NK1s. First, black patients may be less likely than white patients to have access to a home pharmacy due to, for example, lack of convenient transportation.[2, 3] Second, they may be less likely to be able to afford the copayment for an aprepitant prescription.[4] Third, black patients may have limited access to high-quality healthcare facilities, resulting in receipt of lower quality care, including suboptimal CINV prophylaxis. Fourth, providers may have biases, including prejudices, clinical uncertainty, and stereotypes that impact the quality of care they deliver to minority patients.[5] Race may also have an indirect effect on CINV-related healthcare utilization through its effect on antiemetic use. If black patients are less likely to use NK1s and therefore more likely to experience uncontrolled CINV, they may be at increased risk for CINV-related healthcare utilization.

Enabling Resources

Patients' social support (measured as marital status in this analysis) is an important predictor of receipt of and adherence to cancer treatment. Financial resources and socioeconomic status (SES) also affect patients' access to care and their healthcare utilization behavior.[6–8] In this study, SES is measured at the census tract level. These measures include median income and proportion of adult residents without a high school degree. Our study also accounts for patients' receipt of drug copay assistance through Medicare Part D or dual eligibility for Medicaid, which has been shown to improve adherence to prescription medications.[9, 10]

Need

In this study, we controlled for women's need for health services by controlling for their health characteristics, including tumor profile, comorbidities, and age. All women in the study sample have the same clinical need, according to guidelines, for prophylactic NK1 use during their first cycle of chemotherapy because of their receipt of highly emetogenic regimens. However, other health characteristics may influence women's use of healthcare services in Aim 2.

Environment

Previous research suggests that racial disparities in quality of care may be partly explained by the healthcare setting because black patients have less access to high-quality provider groups.[11] In fact, the recent study by Samuel and colleagues found that racial disparities in use of antiemetics were attenuated when hospital fixed effects were included in the analytic model.[12] Because a large proportion of cancer patients receive chemotherapy outside of the hospital, the present analysis cannot account for hospital effects. However, in sensitivity analyses, we attempted to account for variation in prescribing by controlling for provider effects. In our sample, individual providers did not treat sufficient numbers of white and black women to successfully conduct such an analysis, thus the role of provider-level factors in contributing to disparities in NK1 use remains an important area for future research.

Data

The data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.[8] The SEER-Medicare dataset comes from a consortium of population-based cancer registries across the United States linked to Medicare claims for health services obtained from the time of a person's Medicare eligibility until death. The SEER data cover approximately 25% of the U.S. population with cancer and include characteristics of the incident cancer including histology, grade, and stage as well as patient demographic information and vital statistics for people living in California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah, rural Georgia, and metropolitan areas of Atlanta, Detroit, and Seattle. The data include ecological measures of income, education, and other characteristics drawn from the 2000 U.S. Census. Fee-for-service Medicare claims (from Medicare Parts A and B) cover hospital services,

physician services, physician-administered drugs, and other medical services for approximately 70% of Medicare beneficiaries.[9] Medicare Part D claims contain information about prescription drugs obtained from pharmacies.

Sample

We included women aged 65 years and older who were diagnosed with stage I, II, or III breast cancer between January 1, 2007, and December 31, 2011. Eligible women were: (1) not diagnosed at autopsy or death; (2) continuously enrolled in Medicare Parts A and B for 6 months before and 12 months after diagnosis; (3) continuously enrolled in Medicare Part D for 12 months after diagnosis; and (4) not enrolled in an HMO for 6 months before and 12 months after diagnosis. There were 27,160 women meeting these criteria. From this sample, we restricted our analysis to women who received surgery (mastectomy or breast-conserving surgery) and initiated chemotherapy within 6 months of diagnosis (n=4,651). The analysis was further restricted to women whose first cycle of adjuvant chemotherapy included an anthracycline and cyclophosphamide (n=1,569), because guidelines have consistently recommended use of an NK1 for these regimens throughout the study period.[10–14] Because of the small proportion of non-black minorities, the study was restricted to black and white women (n=1,451). Finally, because Part D claims are available starting on January 1, 2007, women in our sample initiated chemotherapy on or after February 1, 2007, so that we could observe Part D claims for antiemetics in the 30 days before chemotherapy initiation (n=1,130). In Aim 3, the sample was further restricted to women initiated chemotherapy before January 1, 2012 (n=1,087), to allow for a year of follow-up. A CONSORT diagram is displayed in Figure 2.

Key Variables

The main independent variable for Aim 1 was patient race (black or white). In Aim 2, both patient race and prophylactic NK1 use were independent variables of interest. In Aim 3, our independent variable was chemotherapy initiation year. Patient-level covariates are drawn from the SEER-Medicare dataset. Specifically, patients' socio-demographic and cancer information are contained in the Patient Eligibility and Diagnosis Summary File (PEDSF) of the SEER-Medicare data. Area-level measures of income and education were drawn from the 2000 U.S. Census. Patients'

comorbidities were measured using data contained in the Medicare Parts A and B claims files and the comorbidity index developed by Klabunde and colleagues.[15]

The dependent variables for all three aims were measured using the Medicare Parts A, B, and D claims files. In Aims 1 and 3, among women beginning their first cycle of highly emetogenic chemotherapy, we assessed the likelihood of using an NK1 for CINV prophylaxis. NK1 users were defined as having a Medicare Part D claim for aprepitant (oral formulation), as identified by the drug name, in the 30 days before or on the day of chemotherapy initiation from the Prescription Drug Events file. Alternatively, they had a Part B claim for aprepitant in the 30 days before or on the day of chemotherapy initiation as identified using Health Care Common Procedure Coding System codes (J8501) and as recorded in the outpatient, physician services, or durable medical equipment claims files. Finally, NK1 users could have a claim for fosaprepitant (IV formulation) (C9242, J1453) on the day of chemotherapy initiation, as recorded in the outpatient or physician services files.

In Aim 2, the dependent variable was any CINV-related utilization, measured as any outpatient or inpatient claims with an associated diagnosis of nausea and vomiting (ICD-9 codes 787.0-787.02), volume depletion (ICD-9 code 276.5), dehydration (ICD-9 code 276.51), or hypovolemia (ICD-9 code 276.52) in the 14 days following chemotherapy administration.[16] The key independent and dependent variables and covariates are summarized in Table 1.

Analytic Approach

The analytic approach for Aims 1, 2, and 3 are outlined below. Overall, we used two approaches to assessing racial disparities. In the primary set of models we implemented the Institute of Medicine's (IOM) definition of a racial healthcare disparity, that is, a difference in treatment not justified by differences in clinical characteristics of the racial groups.[2] Analytic approaches to implement this definition of disparities use statistical models that control only for differences in health status (e.g., co-morbidity, age) and clinical need (e.g., tumor characteristics) and, if available, preferences for care between racial groups. This approach recognizes the mediating role of an individual's SES and related factors, because minorities tend to have lower SES profiles than whites, and that such differences can impact care received. However, such approaches do not adjust for SES-related factors, because doing so may reduce or eliminate the estimated independent effect of

race on care and give a false picture of the care experience of vulnerable patients. [7, 17, 18] Approaches to implement the IOM definition of disparities may also not adjust for other potential mediators of disparities, namely, marital status and geography.[18]

The second, more traditional approach to assessing disparities is to estimate the residual direct effect of race, controlling for all potential mediators of the relationship between race and the outcome, including measures of SES, marital status, and geography. Our secondary models for Aims 1 and 2 used this approach to provide a more conservative estimate of the effect of race on each outcome. In Aim 3, we used only the IOM approach to assessing disparities.

Aim 1: Assess the Relationship Between Patient Race and Prophylactic NK1 Use

First, we examined the distribution of patient characteristics between racial groups using chi-squared tests. We then assessed the relationship between race and prophylactic use of 1) any NK1, 2) aprepitant (oral formulation), and 3) fosaprepitant (IV formulation). To directly estimate risk ratios with robust error variance, we used modified Poisson regression models,[19, 20] estimating generalized linear models with a Poisson distribution and log link. Because black women are disproportionately likely to receive drug copay assistance through Medicaid dual eligibility or a Part D low-income subsidy,[21, 22] we included a drug copay assistance indicator and an interaction of race and copay assistance in our primary NK1 and aprepitant models to determine whether the models should be stratified by drug copay assistance receipt. Because the interaction effect was not statistically significant, we present the main effects models in this dissertation. The empirical models are shown below. Primary models controlled only for patients' clinical characteristics while secondary models also controlled for SES measures and other potential mediators of disparities, including marital status and geography.

Primary model: $NK1\ use = \beta_0 + \beta_1 Race + B_2 Clinical\ Covariates + u$

Secondary model: $NK1\ use = \beta_0 + \beta_1 Race + B_2 Clinical\ Covariates + B_3 SES + B_4 OtherMediatiors + u$

In a sensitivity analysis, we excluded tumor characteristics from the primary NK1 models because these factors should not influence a patient's risk for CINV or need for antiemetics. Further, because advanced stage at diagnosis,[23, 24] hormone receptor negative phenotype, and high grade

are more common in black women,[23, 25] including these covariates might actually attenuate the effect of race on likelihood of receiving CINV prophylaxis.

Aim 2: Assess the Relationship Between Patient Race and CINV-Related Healthcare Utilization

We used modified Poisson regression to assess the relationships between: 1) race and CINV-related healthcare utilization, and 2) NK1 use and CINV-related utilization overall, stratified by race.

Primary model for race and CINV-related utilization: $CINV\text{-}Related\ Utilization = \beta_0 + \beta_1 Race + B_2 Clinical\ Covariates + u$

Secondary model for race and CINV-related utilization: $CINV\text{-}Related\ Utilization = \beta_0 + \beta_1 Race + B_2 Clinical\ Covariates + B_3 SES + B_4 OtherMediatiors + u\ (All)$

Models for NK1 use and CINV-related utilization:
$CINV\text{-}Related\ Utilization = \beta_0 + \beta_1 NK1 + B_2 Clinical\ Covariates + u\ (All)$

$CINV\text{-}Related\ Utilization = \beta_0 + \beta_1 NK1 + B_2 Clinical\ Covariates + u\ (Black)$

$CINV\text{-}Related\ Utilization = \beta_0 + \beta_1 NK1 + B_2 Clinical\ Covariates + u\ (White)$

Aim 3: Assess Longitudinal Trends in Use of NK1s and the Impact of Fosaprepitant Availability on Racial Disparities in Prophylactic NK1 Use

We used modified Poisson regression to estimate changes in NK1 use separately by chemotherapy initiation year. To determine how changes in NK1 use may differ between racial groups, we assessed changes in use of any NK1 and formulation-specific use among black and white patients separately between 2007 and 2011. We controlled for select covariates related to patients' health status and tumor characteristics (patient age, comorbidity burden, and cancer stage).

$NK1\ use = \beta_0 + B_1 ChemoYear + \beta_2 Race + B_3 Clinical\ Covariates + u\ (Black)$

$NK1\ use = \beta_0 + B_1 ChemoYear + \beta_2 Race + B_3 Clinical\ Covariates + u\ (White)$

Expected Outcomes

The expected outcome for Aim 1 was to understand whether racial disparities exist in use of NK1s among women receiving highly emetogenic adjuvant chemotherapy regimens. The existence of disparities may suggest that black patients are receiving inferior CINV prophylaxis, either because their providers are less likely to prescribe appropriate antiemetics or because black patients are less likely to fill their prescriptions. Thus, the results of this aim inform future research to elucidate the

source of disparities in prophylactic NK1 use and the development of interventions to address these disparities. The expected outcome for Aim 2 was to understand the potential impact of disparities in NK1 use in terms of patient outcomes. The results of this aim help establish the significance of potential disparities in antiemetic use in terms of healthcare utilization and potential cost. They may also help inform the design of interventions aimed at reducing avoidable utilization among breast cancer patients. The expected outcome of Aim 3 was to understand whether use of fosaprepitant, compared to oral aprepitant, has increased over time for both racial groups and to understand whether the availability and recommendation of fosaprepitant has helped narrow racial disparities in the use of NK1s. These results fulfill Aim 3's objective of assessing the impact of changes in the formulation and reimbursement of NK1s on disparities in their use and may have implications for providers' prescribing practices and for Medicare reimbursement policy.

Taken together, the results of this study elucidate potential disparities in a critical aspect of supportive breast cancer care. In doing so, they will help transition current cancer disparities research from focusing primarily on curative treatment to also considering supportive care and its implications for patients' QOL and cancer care experience.

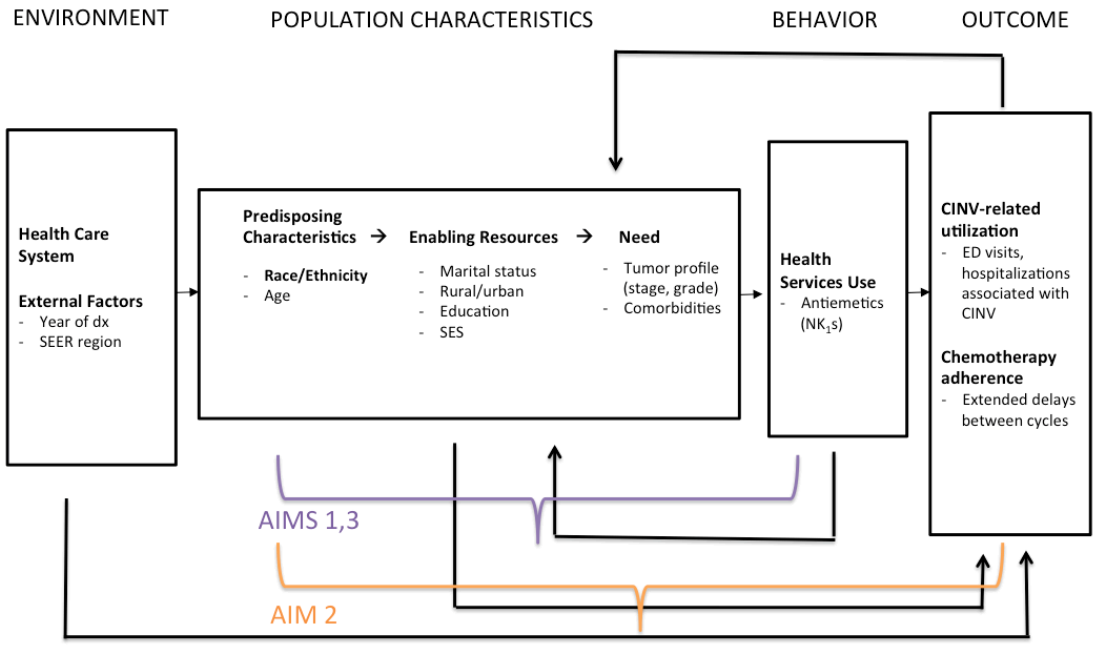

Figure 1. Adapted Andersen Healthcare Utilization Model for NK1 use.

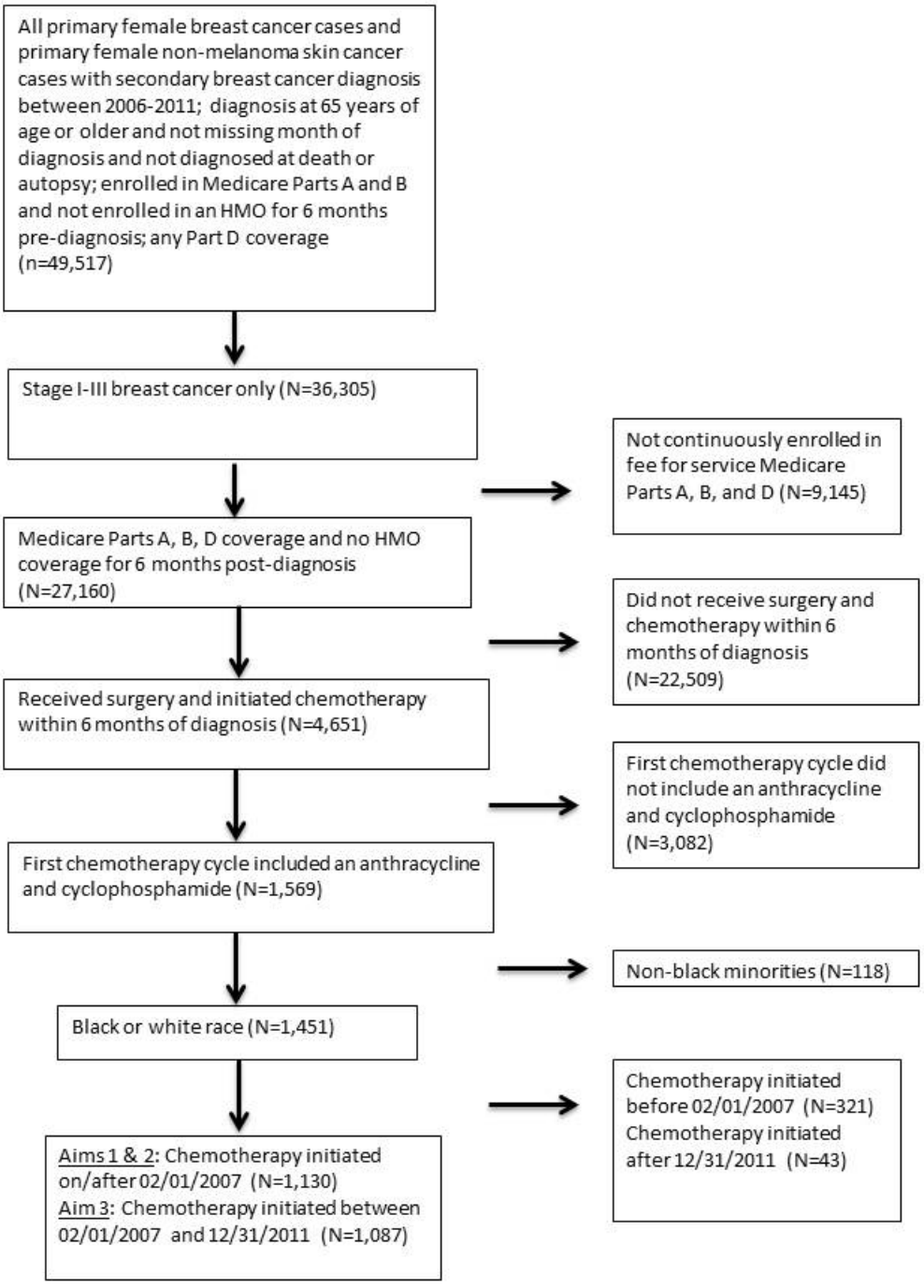

Figure 2. CONSORT diagram showing study inclusion/exclusion criteria.

Table 1. Study Variables for Aims 1, 2, and 3

Variable	Aims	Variable Type	Possible values	Source
Key Independent Variables				
Race	1, 2, 3	Binary	White/Black	Patient Entitlement and Diagnosis Summary File (PEDSF)
NK1 use	2	Binary	Yes/No	Medicare claims
Chemotherapy initiation year	3	Categorical	2007, 2008, 2009, 2010, 2011, 2012	PEDSF
Covariates - Population (Clinical and Demographic) Characteristics				
Age	1, 2, 3	Categorical	65-66; 67-68; 69-71; 72-92	PEDSF
Marital status	1, 2, 3	Binary	Married or partnered/Single	PEDSF
Drug copay assistance receipt (through Medicaid dual eligibility or Part D Low-Income Subsidy)	1, 3	Binary	Yes/No	PEDSF & Part D
% No HS education (Census tract)	1,2,3	Categorical	1.22-9.69%; 9.70-16.57%; 16.58-27.88%; 27.89-75.17%	PEDSF
Median income (Zip code level)	1,2,3	Categorical	$0-32,791; $32,972-44,039; $44,040-58,436; $58,437-188,340	PEDSF
Metropolitan county	1, 2, 3	Binary	Metro/Non-Metro	PEDSF
Comorbidity score	1, 2, 3	Categorical	0/1/2+	Medicare claims
Cancer stage	1, 2, 3	Categorical	I/II/III	PEDSF
Lymph node involvement	1, 2, 3	Binary	Yes/No	PEDSF
Tumor grade	1, 2, 3	Categorical	Low/Intermediate/High	PEDSF
Hormone receptor status	1, 2, 3	Binary	Positive/Negative	PEDSF
Covariates - Environment				
Chemotherapy initiation year	1,2	Categorical	2007-2012	PEDSF
US Region	1,2,3	Categorical	Northeast/Midwest/West/South	PEDSF
Dependent Variables				
NK1 use	1, 3	Binary	Yes/No	Medicare claims
CINV-related utilization	2	Binary	Yes/No	Medicare claims

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CHAPTER 4. INVESTIGATING RACIAL DISPARITIES IN BREAST CANCER PATIENTS' USE OF NK1 RECEPTOR ANTAGONISTS FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Introduction

Patients initiating cancer treatment have consistently cited chemotherapy-induced nausea and vomiting (CINV) as a major and fearful concern.[1] Poorly-controlled CINV can have severe physiological consequences, including dehydration, nutritional derangements, metabolic imbalances, and anorexia.[2] Thus, inadequate CINV control can lead to deterioration of a patient's functional condition and quality of life (QOL). [3–5] Further, hospital admissions, emergency department (ED) visits, and outpatient hospital visits after the first cycle of chemotherapy are both common and costly, with one study estimating the cost of treating CINV between the first and second cycle at $5,299 among patients with a visit and $731 across all patients receiving moderately or highly emetogenic chemotherapy.[6] In addition, uncontrolled CINV can lead to decreased chemotherapy adherence or even withdrawal from potentially beneficial chemotherapy.[2, 7] CINV control is therefore a critical aspect of high-quality cancer care and has profound implications for patients' cancer care experience.

Oncology professional organizations produce and endorse clinical practice guidelines for the use of antiemetics to prevent CINV.[8–10] For several years, the guidelines have recommended prophylactic use of the most potent class of antiemetic, neurokinin-1 recetpor antagonists (NK1s), for patients receiving highly emetogenic chemotherapy. Until 2008, aprepitant, an oral formulation, was the only NK1 available for CINV prophylaxis. Barriers to aprepitant use exist. First, in many cases, patients are required to fill a prescription for aprepitant at their home pharmacy rather than receive it in the clinic at the time of their chemotherapy infusion. Second, the drug is expensive relative to other antiemetics and patients may be subject to high cost-sharing, particularly when the drug is filled at a pharmacy and reimbursed under Medicare Part D. Estimates suggest that three aprepitant capsules cost over $500 under Medicare Part D and patients may be responsible for 25% to 50% of that cost,

depending on their phase of the Part D benefit (i.e., in the initial coverage phase or in the doughnut hole, respectively).[11]

Evidence suggests that cost and access barriers may disproportionately affect minority patients. Studies of patients with lung, prostate, and colorectal cancers have shown black race to be negatively associated with use of other antiemetic drugs.[12, 13] Whether this finding extends to NK1s and to other cancers is unknown. Assessing the relationship between race and NK1 use among breast cancer patients is particularly important because this population frequently receives highly emetogenic chemotherapy. In addition, research has demonstrated that black breast cancer patients may be more likely than white patients to have gaps in or discontinue use of chemotherapy because of hospitalizations and acute illness,[14] possibly due to adverse effects of treatment. In general, minority cancer patients are more likely than white patients to experience uncontrolled symptoms and to report inadequate supportive care for pain and psychosocial symptoms.[15–19] As a first step toward understanding how the quality of CINV prophylaxis may contribute to racial disparities in breast cancer care, we assessed potential racial disparities in prophylactic use of NK1s among early-stage breast cancer patients beginning a chemotherapy regimen for which use of an NK1 is guideline-recommended. We were also interested to learn whether disparities were attenuated by intravenous (versus oral) NK1 use.

Methods

Data

We used the National Cancer Institute's Surveillance Epidemiology and End Result (SEER) database linked with Medicare fee-for-service claims from 2006 to 2012. The SEER program consists of population-based cancer registries and represents 28% of the population with cancer. SEER data are merged with fee-for-service Medicare claims to allow for assessments of health services use among Medicare beneficiaries with cancer.[20] Our study was conducted in accordance with a SEER-Medicare data use agreement and was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Sample

We included women aged 65 years and older who were diagnosed with stage I, II, or III breast cancer between January 1, 2007, and December 31, 2011 (Figure 1). Eligible women were: (1) not diagnosed at autopsy or death; (2) continuously enrolled in Medicare Parts and A and B for 6 months before and 12 months after diagnosis; (3) continuously enrolled in Medicare Part D for 12 months after diagnosis; and (4) not enrolled in an HMO for 6 months before and 12 months after diagnosis. There were 27,160 women meeting these criteria. From this sample, we restricted our study to women who received surgery (mastectomy or breast-conserving surgery) and initiated chemotherapy within 6 months of diagnosis (n=4,651). The analysis was further restricted to women whose first cycle of adjuvant chemotherapy included an anthracycline and cyclophosphamide (n=1,569), because guidelines have consistently recommended use of an NK1 for these regimens throughout the study period.[8–10, 21, 22] Our sample was limited to women initiating adjuvant chemotherapy following surgery (versus women receiving neoadjuvant chemotherapy) in an effort to make the sample as homogenous as possible with regard to treatment experiences and potential unmeasured confounders. Because of the small proportion of non-black minorities (n=118), the study was restricted to black and white women (n=1,451). Finally, we restricted our sample to women who initiated chemotherapy on or after February 1, 2007, so that we could observe Part D prescription drug claims for antiemetics in the 30 days before chemotherapy initiation (n=1,130).

Variables

Our primary outcome was patients' use of an NK1 during the first cycle of adjuvant chemotherapy. NK1 users were defined as having a Medicare Part D claim for aprepitant (oral formulation), as identified by the drug name, in the 30 days before or on the day of chemotherapy initiation. Alternatively, they had a Part B claim for aprepitant in the 30 days before or on the day of chemotherapy initiation, as identified using Health Care Common Procedure Coding System codes (J8501) and as recorded in the outpatient, physician services, or durable medical equipment claims files. Finally, NK1 users could have a claim for fosaprepitant (IV formulation) (C9242, J1453) on the day of chemotherapy initiation, as recorded in the outpatient or physician services files.

Our main independent variable was race (black or white), as reported in the Patient Entitlement and Diagnosis Summary File. Covariates included patients' demographic and clinical characteristics: age, cancer stage, tumor grade, hormone receptor status, lymph node involvement, and comorbid illness (calculated using the Klabunde modification of the Charlson score based on patients' Medicare Part A and B claims pre-diagnosis).[23] We also measured marital status and receipt of a low-income subsidy to assist with prescription drug costs (i.e., Medicaid dual eligibility and/or "extra help" through the Medicare Part D program). Although patients dually eligible for Medicare and Medicaid receive subsidies to assist with drug co-pays, their prescription drugs are typically covered under Medicare Part D versus Medicaid. Other measures of socioeconomic status (SES) included census tract–level high school completion rate and median income, obtained from the 2000 census. Geographic variables were U.S. region of residence and extent of urbanization at patients' residences.

Statistical Analysis

We compared the distributions of patient characteristics between racial groups using chi-squared tests. To directly estimate relative risk with robust error variance, we used modified Poisson regression[24] to assess the relationship between race and NK1 use controlling for pre-specified patient characteristics. Because black women are disproportionately likely to receive drug copay assistance through Medicaid dual eligibility or a Part D low-income subsidy,[25, 26] we included a drug copay assistance indicator and an interaction of race and copay assistance in our primary models to determine whether the models should be stratified by drug copay assistance receipt. Because the interaction effect was not statistically significant, we present the main effects models. Specifically, we present risks and adjusted risk ratios (aRR) with 95% confidence intervals (CI) for NK1 use, comparing black and white women. We estimated separate models for any NK1 use, aprepitant use, and fosaprepitant use. Because fosaprepitant was not approved by the FDA until 2008, this model was limited to patients who initiated chemotherapy in 2009 or later (N=524).

Accounting for Socioeconomic Status. The Institute of Medicine (IOM) defines racial healthcare disparities as differences in treatment not justified by racial differences in health status or preferences. [27] Analytic approaches to implement this definition of disparities use statistical models

that control only for differences in health status (e.g., co-morbidity, age), clinical need (e.g., tumor characteristics) and, if available, preferences for care between racial groups.[13, 28, 29] This approach recognizes the mediating role of an individual's SES and SES-related factors, because minorities tend to have lower SES profiles than whites and such differences can impact care received. Therefore, the IOM's model does not adjust for SES-related factors because doing so may reduce or eliminate the estimated independent effect of race on care and give a false picture of the care experience of vulnerable patients. In accordance with the IOM definition of healthcare disparities, our primary models adjusted for clinical characteristics, namely: age, year of chemotherapy initiation, tumor characteristics, and medical comorbidity.[29] In secondary analyses we assessed whether our findings would differ when including census tract–level SES, marital status, or geography in the primary model.

Sensitivity Analyses

In an exploratory model, we excluded tumor characteristics because these factors should not influence a patient's need for antiemetics. Further, because advanced stage at diagnosis,[30, 31] hormone receptor negative phenotype and high grade are more common in black women,[30, 32] including these covariates might actually attenuate the effect of race on likelihood of receiving CINV prophylaxis. Results from these analyses were consistent with the primary analysis and are not shown.

Results

Among the 1,130 women who met our eligibility criteria, 1,015 (89.8%) were white. Compared to white women, black women were less likely to be married (25% versus 53%) and more likely to receive drug copay assistance through Medicaid or Medicare Part D (70% versus 21%). There were also racial differences in census tract–level income and education and U.S. region of residence (see Table 2).

In the unadjusted analyses, we found statistically significant racial differences in women's use of any NK1 (41% white vs. 28% black; $p<0.01$) and aprepitant use (29% white vs. 16% black, $p<0.01$), but not in fosaprepitant use (15% white vs. 12% black, $p=0.41$). Unadjusted associations of each covariate with NK1, aprepitant, and fosaprepitant use are shown in Table 3.

In models adjusting for clinical characteristics only, racial disparities remained in use of any NK1 (aRR: 0.68, 95% CI: 0.51-0.91) and aprepitant (aRR: 0.54, 95% CI: 0.35-0.83). The relationship between race and fosaprepitant use was non-significant (aRR: 0.82, 95% CI: 0.51-1.33) (see Table 4). Secondary models that included measures of SES (census tract–level income and education and drug copay assistance receipt), marital status, and geographic factors were consistent with our primary models, however estimates were no longer statistically significant. Being black reduced the risk of using any NK1 by 19% (aRR: 0.81, 95%CI: 0.60-1.10; NS) and aprepitant by 32% (aRR: 0.66 95% CI: 0.43-1.104; NS)) (see Table 4).

Discussion

Among women initiating highly emetogenic chemotherapy containing an anthracycline and cyclophosphamide for their early-stage breast cancer, we observed that black women had a 32% decreased risk of using any NK1 for the prevention of CINV. When examining oral and intravenous NK1 formulations separately, black women had a 46% decreased risk of receiving oral aprepitant. We did not observe a statistically significant racial difference in women's receipt of intravenous fosaprepitant. When we added SES- and geography-related variables to our models, the relationships between race and NK1 use and race and aprepitant, the effect estimates remained consistent with disparities but were no longer statistically significant.

Despite clinical guidelines recommending the use of NK1s for anthracycline- and cyclophosphamide-containing breast cancer regimens throughout the study period, only 40% of women in our sample used an NK1, according to our definition of prophylactic use. This may be due to a lack of provider familiarity with recommendations for NK1s for the chemotherapy regimens we examined or institutional policies' failure to include NK1s in the antiemetic order sets for these chemotherapy regimens. Although guidelines have consistently recommended use of an NK1 for anthracycline- and cyclophosphamide-containing breast cancer regimens throughout our study period, in earlier guidelines, these regimens were classified as "moderately" emetogenic; later in the study period, guideline updates reclassified the regimens as "highly" emetogenic.[8–10] This explanation is consistent with the substantial increase in NK1 use over time that we observed.

Our finding of a disparity is consistent with the limited research to date examining variation in use of antiemetics for CINV prevention. However, to our knowledge, our study is the first to include NK1s. In the only study to date that specifically investigated racial disparities in antiemetic use, Samuel et al. focused on patients with colorectal, prostate, and lung cancers in the Veterans Affairs system.[13] Although they documented disparities in use of some antiemetics, their data were from the early 2000s, before NK1s were recommended by clinical guidelines for the prevention of CINV. Gomez and colleagues explored patterns of guideline-concordant antiemetic use among lung cancer patients.[12] Although not focused on disparities, the authors demonstrated racial and income differences in antiemetic use. However, this study was limited to a single state's cancer registry and did not include NK1s in the analysis.

Our study is also the first of which we are aware to examine patterns of use of oral versus intravenous NK1s. It is important to distinguish between formulations because many patients are required to fill a prescription for oral aprepitant, a high-cost medication, at their home pharmacy. Under Medicare Part D, patients may be subject to high cost-sharing. The introduction of intravenous fosaprepitant in 2008 may have helped obviate access and cost barriers related to use of oral therapy. Specifically, because fosaprepitant is administered in the clinic, it is covered under Medicare Part B. Although Part B tends to have 20% co-insurance for all services, a large majority of Medicare beneficiaries have supplemental insurance coverage to assist with their out-of-pocket Part B costs.[33] Our identification of racial disparities in oral but not intravenous NK1 use supports the hypothesis that fosaprepitant is more affordable and accessible for patients. However, it is important to acknowledge that the lack of an observed disparity in fosaprepitant use could be due to insufficient sample size, because the fosaprepitant models were limited to patients who initiated chemotherapy in 2009 or later (N=524).

Two potential explanations for our observation of disparities in aprepitant use are that black women are: (1) equally as likely as white women to be prescribed aprepitant but less likely to fill their prescriptions, possibly due to financial or other access barriers or (2) disproportionately likely to see providers who do not prescribe NK1s in accordance with clinical guidelines because they are more likely to be treated in lower-performing settings.[13, 34] Both explanations seem plausible given our

findings. Specifically, the fact that disparities in NK1 and aprepitant use were somewhat attenuated when SES-related factors were added to the models suggests that the disparities are at least partly explained by SES differences between black and white women. These SES differences could translate into differential ability to pay for prescription drugs or differential access to high-quality care (including guideline-adherent antiemetic prescribing).[13, 34] Interestingly, geographic region also appeared to partly attenuate disparities, suggesting a potential role for geographic variation in prescribing in explaining disparities in NK1 use.

Also of note, unlike prior reports, receipt of drug copay assistance appeared to act as an indicator of low income rather than as an indicator of increased ability to pay for prescription drugs. Specifically, recent work by Neuner and Biggers documented a positive effect of drug copay assistance receipt on breast cancer patients' adherence to aromatase inhibitors.[25, 35] In contrast, we observed a negative effect of drug copay assistance receipt on aprepitant use. One possible explanation for this difference may be our measure of drug copay assistance receipt, which combined assistance through Medicaid dual eligibility and the Part D low-income subsidy (i.e., a woman was said to be a drug copay assistance recipient if she received either type of assistance), whereas Neuner and Biggers's studies measured only Part D low-subsidy receipt. Our results may reflect the mixed effect of dual eligibility status, which could be an indicator of decreased access, and Part D low-income subsidy receipt, which has been demonstrated to improve adherence.

Our study had several limitations. First, we focused on fee-for-service Medicare beneficiaries with Part D coverage. It is unknown whether our findings generalize to younger women, Medicare beneficiaries enrolled in an HMO, or women without prescription drug coverage through Part D. Second, in our secondary models, we may have misclassified individuals' SES by using area-level measures of SES.[36, 37] Third, because of the limited number of minority women represented in SEER-Medicare, we may have lacked statistical power for some comparisons. This is particularly true of the fosaprepitant models, which were limited to the 524 women who initiated chemotherapy in 2009 or later. Fourth, our use of Medicare administrative claims data for this analysis may have resulted in our under-capturing of NK1 use overall if these medications were provided in clinic and not billed to Medicare. However, we do not believe that capture issues would differentially affect black

versus white patients, so comparisons between groups should be valid nonetheless. Fifth, with claims data, we could not separate physicians' failure to prescribe aprepitant from patients not filling prescriptions. Thus, although we have documented the existence of disparities, we are unable to identify the underlying causes of the observed disparities using SEER-Medicare data. Future studies should attempt to use clinical data to ascertain whether the disparities identified here reflect disparities in NK1 prescriptions or fills. If black and white women are equally likely to be prescribed NK1s but less likely to fill these prescriptions, disparities may in fact reflect barriers related to affordability and accessibility.

Although our study and others have pointed to racial disparities in use of antiemetics to prevent CINV, it remains unclear whether such disparities contribute to the disparate outcomes of black and white cancer patients. In breast cancer, black-white disparities in systemic treatment adherence and survival have been documented.[14, 38–40] Future studies should assess the role of treatment-induced side effect (including CINV) prevention and management in contributing to potential disparities not only in these observed outcomes but also in patients' quality of life and cancer care experience.

Our findings suggest that there may be a need for increased awareness among oncology providers of potential barriers to obtaining oral medications for CINV prevention. In addition, our data point to several possible explanations for and points of intervention to reduce disparities. For example, disparities may stem from low income and minority patients' difficulty accessing or affording oral aprepitant, in which case the IV formulation may be more appropriate. Disparities may also stem from variation in prescribing, in which case provider-targeted interventions may help reduce disparities. To inform specific solutions, further research is needed to determine the relative contribution of patient-, provider-, and system-level factors to disparities.

Table 2. Aim 1 Sample Characteristics, by Race

	White (N=1,015)	Black (N=115)	p-value
Demographic Characteristics (%)			
Age at Cancer Diagnosis			
65-66	20.7	25.2	0.7
67-68	24.7	24.4	
69-71	25.1	22.6	
72-91	29.4	27.8	
Marital Status at Diagnosis[a]			
Married/Partnered	52.9	25.2	**<0.0001**
Non Married/Partnered	42.5	--	
Unknown	4.6	--	
Median Household Income in Census Tract of Residence[a]			
$0-32,791	21.6	53.0	**<0.0001**
$32,972-44,039	25.5	--	
$44,040-58,436	--	13.0	
$58,437-188,340	27.1	--	
Unknown	--	0	
Proportion of Adult Residents with No High School Degree in Census Tract of Residence[a]			
1.22-9.69%	27.4	--	**<0.0001**
9.70-16.57%	26.7	--	
16.58-27.88%	--	30.4	
27.89-75.17%	20.3	57.4	
Unknown	--	0	
Drug Copay Assistance (Medicaid Dual Eligibility and/or Part D Low Income Subsidy)			
Yes	21.1	69.6	**<0.0001**
No	78.9	30.4	
Residence			
Metropolitan County	74.8	82.6	0.06
Non-Metropolitan County	25.1	16.4	
U.S. Region			
Northeast	19.4	20.0	**<0.0001**
Midwest	18.0	14.8	
West	37.4	14.8	
South	25.1	50.4	
Clinical Characteristics			
Year of Chemotherapy Initiation[a,b]			
2007	28.9	31.3	0.9
2008	20.1	20.9	

2009	17.0	18.3	
2010	14.8	--	
2011	15.4	14.8	
2012	3.8	--	
Charlson Comorbidity Score[a]			
0	78.4	75.7	0.2
1	17.2	--	
>1	4.3	--	
Cancer Stage			
Stage I	12.8	10.4	0.7
Stage II	53.6	56.5	
Stage III	33.6	33.0	
Hormone Receptor Status			
HR positive	67.0	62.6	0.5
HR negative	28.7	--	
Unknown	3.7	--	
Tumor Grade[a]			0.3
Low	10.3	--	
Intermediate	40.1	33.9	
High	45.9	56.5	
Unknown	4.3	--	
Lymph Node Involvement[a]			
Yes	70.9	67.0	0.06
No	27.7	--	
Unknown	1.4	--	

[a] Cells containing proportions that reflect Ns<11 or information that would allow Ns<11 to be derived have been suppressed (--) to protect patients' identities

[b] A small proportion of patients initiated chemotherapy in 2012 because we only have SEER data on patients diagnosed through December 2011. Thus, only patients who received chemotherapy within the first 6 months of 2012 are included in our sample.

Table 3. Unadjusted Associations of Race and Covariates with NK1 Use

	NK1 Users (N=425)		Aprepitant Users (N=290)		Fosaprepitant Users (N=167)	
Demographic Characteristics (%)						
Race		*p-value*		*p-value*		*p-value*
Black					12.2	0.4
White	27.8	**<0.01**	15.7	**<0.01**	15.1	
Age at Cancer Diagnosis	41.0		29.2			
65-66					14.2	0.4
67-68	39.7	0.4	28.9	0.2	17.9	
69-71	42.3		29.0		13.8	
72-91	41.5		30.5		13.3	
Marital Status at Diagnosis	35.8		23.6			
					16.3	0.4
Married/Partnered						
Non Married/Partnered	41.2	0.4	28.6	0.6	13.5	
Missing	37.6		26.5		11.8	
Median Household Income in Census Tract of Residence						
$0-32,791	31.4	**<0.0001**	19.2	**<0.0001**	14.3	0.6
$32,972-44,039	34.9		24.3		12.7	
$44,040-58,436	39.6		26.1		15.0	
$58,437-188,340	52.3		40.2		17.4	
Proportion of Adult Residents with No High School Degree in Census Tract of Residence[1]						
					17.7	0.6
1.22-9.69%	51.8	**<0.0001**	39.0	**<0.0001**		
9.70-16.57%	38.1		26.7		13.9	
16.58-27.88%	36.2		22.6		14.3	
27.89-75.17%	31.2		20.6		13.2	
Drug Copay Assistance (Medicaid Dual Eligibility and/or Part D Low Income Subsidy)						
Yes					10.2	**0.01**
No	28.2	**<0.0001**	20.4	**<0.01**	16.4	
Residence	43.6		30.4			
Metropolitan County					15.3	0.4
Non-Metropolitan County	42.6	**<0.001**	30.2	**<0.01**	13.0	
U.S. Region	30.4		20.3			
Northeast					14.1	0.1
Midwest	50.0	**<0.01**	39.6	**<0.001**	16.5	
West	50.0		22.0		11.8	
South	39.0		30.2		17.9	
Clinical Characteristics	35.8		20.1			
Year of Chemotherapy						

Initiation						
2007					N/A	**<0.001**
2008					N/A	
2009	24.3	**<0.0001**	24.3	0.12	16.5	
2010	30.3		29.8		20.9	
2011	41.2		31.4		42.8	
2012	43.6		32.5		60.5	
Charlson Comorbidity Score	65.9		26.0			
0	76.7		14.3		14.8	0.4
1					12.9	
>1	40.8	0.3	29.1	0.06	20.8	
Cancer Stage	35.6		25.3			
Stage I	35.9		15.1		14.8	0.9
Stage II					14.6	
Stage III	39.4	0.9	26.1	0.9	15.0	
	39.2		27.9			
Hormone Receptor Status	40.4		28.2			
HR positive					13.2	**0.03**
HR negative					19.1	
Status unknown/missing	44.5	0.1	27.4	0.7	10.4	
Tumor Grade	37.5		27.9			
Low					15.0	0.4
Intermediate	40.7	0.3	31.2	0.6	12.5	
High	36.3		26.9		16.4	
Unknown/missing	42.4		28.1		--	
Lymph Node Involvement						
Yes	39.8	0.2	28.6	0.3	14.3	0.3
No	38.2		25.2		15.3	

Table 4. Adjusted Risks and Risk Ratios of Any NK1 Use, Aprepitant Use, and Fosaprepitant Use

	Primary Models (adjusting for clinical characteristics only)	**Secondary Models (adjusted for SES-related variables)**
	Estimate and 95% CI	Estimate and 95% CI
Risk NK1 use, white	0.30 (0.20-0.44)	0.37 (0.21-0.63)
Risk NK1 use, black	0.21 (0.13-0.33)	0.30 (0.16-0.55)
Risk ratio NK1 use, black v. white	**0.68 (0.51-0.91)**	0.81 (0.60-1.10)
Risk aprepitant use, white	0.29 (0.18-0.46)	0.36 (0.18-0.55)
Risk aprepitant use, black	0.15 (0.08-0.30)	0.24 (0.10-0.55)
Risk ratio aprepitant use, black v. white	**0.54 (0.35-0.83)**	0.66 (0.43-1.04)
Risk fosaprepitant use, white	0.25 (0.13-0.50)	0.25 (0.09-0.70)
Risk fosaprepitant use, black	0.21 (0.10-0.45)	0.26 (0.09-0.82)
Risk ratio fosaprepitant use, black v. white	0.82 (0.51-1.33)	1.05 (0.62-1.76)

Table 5. Full Results of Primary Modified Poisson Regression Models, Adjusted Risk Ratios and 95% Confidence Intervals for NK1 Use

	Any NK1 Use	**Aprepitant Use**	**Fosaprepitant Use**
Demographic Characteristics			
Race			
White	1.00 (REF)	1.00 (REF)	1.00 (REF)
Black	**0.68 (0.51-0.91)**	**0.54 (0.35-0.83)**	0.82 (0.51-1.33)
Age at Cancer Diagnosis			
65-66	1.00 (REF)	1.00 (REF)	1.00 (REF)
67-68	0.94 (0.87-1.29)	1.01 (0.77-1.31)	1.28 (0.91-1.83)
69-71	1.06 (0.87-1.29)	1.04 (0.80-1.35)	1.04 (0.71-1.52)
72-91	0.89 (0.73-1.09)	0.81 (0.62-1.08)	0.96 (0.67-1.37)
Clinical Characteristics			
Year of Chemotherapy Initiation			
2007	1.00 (REF)	1.00 (REF)	**--**
2008	1.24 (0.95-1.42)	1.20 (0.92-1.58)	--
2009	**1.70 (1.32-2.19)**	1.29 (0.97-1.71)	1.00 (REF)
2010	**1.75 (1.36-2.26)**	1.30 (0.97-1.74)	1.26 (0.81-1.95)

2011	**2.72 (2.20-3.38)**	1.08 (0.79-1.48)	**2.63 (1.83-3.78)**
2012	**3.15 (2.48-4.02)**	0.67 (0.33-1.35)	**3.66 (2.46-5.45)**
Charlson Comorbidity Score			
0	1.00 (REF)	1.00 (REF)	1.00 (REF)
1	0.88 (0.73-1.07)	0.88 (0.68-1.15)	0.90 (0.62-1.29)
>1	0.84 (0.61-1.15)	0.56 (0.30-1.06)	1.10 (0.71-1.70)
Cancer Stage			
Stage I	1.00 (REF)	1.00 (REF)	1.00 (REF)
Stage II	0.98 (0.76-1.26)	1.06 (0.73-1.53)	1.04 (0.65-1.65)
Stage III	0.95 (0.71-1.28)	1.02 (0.67-1.56)	0.98 (0.57-1.69)
HR Status			
HR negative	1.00 (REF)	1.00 (REF)	1.00 (REF)
HR positive	**0.80 (0.68-0.94)**	0.91 (0.71-1.15)	**0.64 (0.48-0.85)**
Tumor Grade			
Low	1.00 (REF)	1.00 (REF)	1.00
Intermediate	0.88 (0.69-1.13)	0.86 (0.63-1.17)	0.75 (0.48-1.15)
High	0.92 (0.72-1.19)	0.90 (0.63-1.24)	0.73 (0.47-1.12)
Lymph Node Involvement			
No	1.00 (REF)	1.00 (REF)	1.00 (REF)
Yes	1.16 (0.95-1.42)	1.18 (0.88-1.58)	1.09 (0.77-1.55)

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CHAPTER 5. EXAMINING RACIAL VARIATION IN ANTIEMETIC USE AND POST-CHEMOTHERAPY HEALTHCARE UTILIZATION FOR NAUSEA AND VOMITING AMONG BREAST CANCER PATIENTS

Introduction

In the United States, breast cancer is the most common malignancy among women.[1] Over the past two decades, advancements in early detection and treatment have improved breast cancer outcomes, leading to five-year survival rates of 99% for local-stage disease and 85% for regional-stage disease.[2] With these advances, the goals of breast cancer care have expanded from treating the disease to preserving women's quality of life (QOL) during treatment. QOL is conceptualized as a multidimensional measure of physical, functional, emotional, and social well-being.[3] The presence of symptoms related to breast cancer and its treatment is an important component of QOL.[4, 5] Thus, symptom management is increasingly recognized as critical to high-quality breast cancer care.[6–8]

Research suggests that cancer patients of minority race may receive inadequate symptom management. Studies have documented racial/ethnic disparities in outcomes related to symptom burden and severity,[9, 10] adequacy of pain treatment,[11–13] and patients' perceived unmet need for supportive care.[14] Other studies have demonstrated that minority patients may underuse medications to control treatment-related symptoms. In particular, evidence suggests that black patients may be more likely than white patients to experience underuse of guideline-recommended antiemetic medications to prevent chemotherapy-induced nausea and vomiting (CINV), which cancer patients have consistently cited as a major and fearful concern.[15] Specifically, Samuel and colleagues found that among colorectal, lung, and prostate cancer patients being treated with chemotherapy in the Veterans Affairs system, black patients were less likely than white patients to use 5HT3 receptor antagonists.[16] Gomez and colleagues also found racial and income disparities in use of both 5HT3 antagonists and dexamethasone among lung cancer patients in Texas.[17] More recently, we documented disparities in use of NK1s, a newer and more potent class of antiemetics

recommended for use with highly emetogenic chemotherapy regimens among women with early-stage breast cancer, a population that frequently receives highly emetogenic chemotherapy.[18]

In addition to the known implications for patients' QOL, racial disparities in CINV prophylaxis may perpetuate well-documented disparities in other dimensions of breast cancer care. Namely, research has demonstrated that black women may be less likely to adhere to recommended chemotherapy regimens and schedules[19–22] and more likely to experience hospitalizations and acute illness during treatment with chemotherapy.[22] Others have suggested that minority women's difficulty accessing medications to control treatment-related side effects may help explain differential treatment experiences.[23] However, the link between disparities in side effect control and treatment experiences of breast cancer patients has not been empirically studied.

With the objective of furthering understanding of how racial disparities in CINV management may contribute to racial disparities in breast cancer treatment experiences, we assessed racial differences in post-chemotherapy healthcare utilization related to CINV, including use of inpatient, emergency department, or outpatient services. We also assessed the role of prophylactic NK1 use in potentially attenuating these differences. Finally, we assessed racial differences in any post-chemotherapy healthcare utilization overall and for other common breast cancer treatment-induced side effects to determine whether any potential differences in utilization for CINV could be explained by differential use of services more broadly.

Methods

Data

We used the National Cancer Institute's Surveillance Epidemiology and End Result (SEER) database linked with Medicare fee-for-service claims from 2006 to 2012. The SEER program consists of population-based cancer registries and represents 28% of the population with cancer. SEER data are merged with fee-for-service Medicare claims.[24] Data for our analysis came from the Prescription Drug Event records, the Medicare Provider Analysis and Review (MEDPAR) file for inpatient services, the Hospital Outpatient Standard Analytic file for outpatient facility services, the 100% Physician/Supplier file for physicians' services, and the Durable Medical Equipment (DME) File.

Our study was conducted in accordance with a SEER-Medicare data use agreement and was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Sample

We included women aged 65 years and older who were diagnosed with stage I, II, or III breast cancer between January 1, 2007, and December 31, 2011. Eligible women were: (1) not diagnosed at autopsy or death; (2) continuously enrolled in Medicare Parts A and B for 6 months before and 12 months after diagnosis; (3) continuously enrolled in Medicare Part D for 12 months after diagnosis; and (4) not enrolled in an HMO for 6 months before and 12 months after diagnosis. There were 27,160 women meeting these criteria. From this sample, we restricted our analysis to women who received surgery (mastectomy or breast-conserving surgery) and initiated chemotherapy within 6 months of diagnosis (n=4,651). The analysis was further restricted to women whose first cycle of adjuvant chemotherapy included an anthracycline and cyclophosphamide (n=1,569) because guidelines have consistently recommended use of an NK1 for these regimens throughout the study period.[25–29] Due to of the small proportion of non-black minorities (n=118), the study was restricted to black and white women (n=1,451). Finally, because Part D claims are available starting on January 1, 2007, women in our sample initiated chemotherapy on or after February 1, 2007 (n=1130). This enabled us to observe Part D claims for antiemetics in the 30 days before chemotherapy initiation.

Variables

The primary outcome was post-chemotherapy healthcare use, measured as any inpatient or outpatient claims (including emergency department claims) in the 14 days after the first chemotherapy infusion. We were specifically interested in CINV-related use, identified by claims with an associated diagnosis of nausea and vomiting (ICD-9 codes 787.0-787.02), volume depletion (ICD-9 code 276.5), dehydration (ICD-9 code 276.51), or hypovolemia (ICD-9 code 276.52) in the 14 days after the first chemotherapy infusion. We chose 14 days as the window of observation because adjuvant chemotherapy regimens for breast cancer should be given no more frequently than every 14 days.[30]

The main independent variables in our analysis were race (black or white), as reported in the Patient Entitlement and Diagnosis Summary File (PEDSF) of the SEER-Medicare data, and

prophylactic NK1 use. NK1 users were defined as having a Medicare Part D claim for aprepitant (oral formulation), as identified by the drug name, in the 30 days before or on the day of chemotherapy initiation. Alternatively, they had a Part B claim for aprepitant in the 30 days before or on the day of chemotherapy initiation, as identified using Health Care Common Procedure Coding System codes (J8501) and as recorded in the outpatient, physician services, or durable medical equipment claims files. Finally, NK1 users could have a claim for fosaprepitant (IV formulation) (C9242, J1453) on the day of chemotherapy initiation, as recorded in the outpatient or physician services files. We focused on the first cycle of chemotherapy because we were interested in measuring use of NK1s for CINV prophylaxis rather than use that may be in response to symptoms experienced during a previous cycle.

Covariates included patients' demographic and clinical characteristics: age at diagnosis, American Joint Committee on Cancer stage, tumor grade, hormone receptor status, lymph node involvement, comorbid illness (calculated using the Klabunde modification of the Charlson score based on patients' Medicare Part A and B claims pre-diagnosis),[31] and year of chemotherapy initiation. We also included information on patients' marital status. Area-level measures of socioeconomic status (SES) included census tract–level high school completion rate and median income, obtained from the 2000 census. Geographic variables were U.S. region of residence and extent of urbanization in patients' neighborhoods.

Statistical Analysis

We examined the distribution of patient characteristics between racial groups using chi-squared tests. To directly estimate risk ratios with robust error variance, we used modified Poisson regression [32] to assess the relationships between race, NK1 use, and post-chemotherapy healthcare utilization, controlling for relevant patient characteristics. We present unadjusted risk ratios (RR) and adjusted risk ratios (aRR) with 95% confidence intervals (CI) for post-chemotherapy healthcare utilization, comparing black and white women and NK1 users versus non-users.

Accounting for SES. The Institute of Medicine (IOM) defines racial healthcare disparities as differences in treatment not justified by racial differences in health status or preferences.[33] Analytic approaches to implement this definition use statistical models that control only for differences in

health status (e.g., comorbidity, age) and clinical need (e.g., tumor characteristics) and, if available, preferences for care between racial groups.[16, 34, 35] This approach recognizes the mediating role of an individual's SES and SES-related factors, that is, minorities tend to have lower SES profiles than whites and such differences can impact care received. However, such approaches do not adjust for SES-related factors because doing so may reduce the estimated independent effect of race on care and give a false picture of the care experience of racial minority patients.

Consistent with the IOM definition of healthcare disparities, our primary models adjusted for clinical characteristics (age at diagnosis, year of chemotherapy initiation, tumor characteristics, and medical comorbidity).[35] We did not adjust for census tract–level measures of SES or in our primary models; neither did we adjust for other potential mediators of disparities, namely geographic factors (U.S. region of residence and metropolitan versus non-metropolitan residence) and marital status. However, because it is important to understand where disparities in care might arise, we conducted secondary analyses to assess whether differences in census tract–level SES, marital status, or geography attenuated potential racial differences in utilization.

Sensitivity Analyses

Sensitivity analyses restricted the outcome measurement window to 7 days post-chemotherapy administration and restricted CINV-related utilization to claims with a primary or secondary diagnosis related to CINV.

Results

Among the 1,130 women who met our eligibility criteria, 1,015 (89.8%) were white and 115 (10.2%) were black. Compared to white women, black women were more likely to be single (71% versus 42%, $p<0.0001$). There were also racial differences in census tract–level income and education and U.S. region of residence ($p<0.0001$). Regarding CINV prophylaxis, black women were 10.9% less likely to use an NK1 ($p<0.05$) (Table 6). Overall, 91% of women had outpatient visits in the 14 days following their first chemotherapy infusion and 23% of women were treated for CINV. CINV-related utilization consisted largely of claims for outpatient visits (22%); only 2% of women had ED or inpatient claims related to CINV.

CINV-Related Utilization

In unadjusted analysis, compared to white women, black women had a 37% decreased risk of experiencing any CINV-related utilization (RR: 0.63, 95% CI: 0.40-0.99) (Table 2). Racial differences in CINV-related utilization did not persist in our primary model adjusting for clinical characteristics (aRR: 0.66, 95% CI: 0.42-1.04, p=0.07) or in the secondary model adjusting for clinical characteristics along with SES, marital status, and geographic variables (aRR: 0.69, 0.42-1.14, p=0.12). In both adjusted models, estimates were similar to the unadjusted results, but they were no longer statistically significant due to widening confidence intervals.

Patients' NK1 use was positively associated with CINV-related utilization in unadjusted and adjusted models. Compared to women who did not receive an NK1 for the prevention of CINV, women who did experienced an increased risk of CINV-related utilization (aRR: 1.34, 95%CI: 1.07-1.68, p=0.01). This positive relationship persisted among white women (aRR: 1.33, 95%CI: 1.06-1.69, p=0.01) but it was not statistically significant among black women (aRR: 1.08, 95% CI: 0.34-3.41, p=0.90) (data not shown).

In the sensitivity analysis restricting CINV-related utilization to claims with a primary or secondary (versus any) diagnosis code related to CINV, the racial difference in utilization was larger than in the primary model, but still statistically non-significant (aRR: 0.52, 95% CI: 0.26-1.05; p=0.07). In an additional sensitivity analysis restricting the window of observation for CINV-related claims to 7 days post-chemotherapy initiation, estimates were similar to those of the main model (aRR: 0.61, 95% CI: 0.25-1.47, p=0.30).

Other Post-Chemotherapy Utilization

In analyses examining racial differences in any post-chemotherapy healthcare utilization, we found no differences in either unadjusted or adjusted models (aRR: 0.95, 95%CI: 0.89-1.03, p=0.21) (Table 7). There were also no statistically significant racial differences in women's outpatient utilization for other common chemotherapy-induced side effects. Specifically, black women were no less likely than white women to receive treatment for neutropenia (aRR: 0.90, 95% CI: 0.71-1.16, p=0.42) or fatigue (aRR: 0.45, 95% CI: 0.14-1.44, p=0.18).

Discussion

We observed possible racial variation in use of outpatient services for CINV during the first cycle of highly emetogenic chemotherapy, with black women being less likely to receive CINV-related care in the post-chemotherapy period. This finding was counter to our hypothesis that black women would be more likely to experience CINV-related utilization because of evidence of potential underuse of NK1s for CINV prophylaxis among black patients. Instead, in this SEER-Medicare sample, black women were at lower risk for both using an NK1 and for receiving treatment for CINV. Although the racial difference in CINV-related utilization was not statistically significant after adjustment for covariates, estimates were still consistent with lower utilization among black patients. This racial difference did not extend to any post-chemotherapy outpatient utilization. There are several potential explanations for our findings.

One explanation for racial variation in cancer-related health services use is that black cancer patients are less likely to access care in general,[33] for example, adjuvant treatment for breast cancer.[36] Similar patterns have been observed in other cancers, with black patients more likely to refuse lung cancer treatment.[37] However, it seems unlikely that racial differences in care-seeking behavior fully explain the variation we observed because our sample is limited to women who underwent surgery and initiated adjuvant chemotherapy. Moreover, we observed no racial variation in the use of any outpatient services during the 14 days following chemotherapy initiation. This suggests that even among women who chose to undergo multi-model therapy, differences in CINV-related healthcare utilization exist.

Because racial differences in general or cancer care–seeking behavior do not appear to explain racial variation in CINV-related services use, it may be that the variation we observed is specific to CINV or symptom management. There are two reasons black women may be less likely to have claims with diagnosis codes related to CINV. First, black and white women may be at equal risk of experiencing CINV but black women may be less likely to report this experience to their providers.[38] Differential reporting could result from differential thresholds for reporting symptoms across demographic or cultural characteristics.[39] Alternatively, minority and low-income women may have competing health or social concerns that affect their likelihood of reporting symptoms

and/or prioritizing their management.[39] Others have suggested that vulnerable populations, including minorities, may receive suboptimal care due to decreased self-efficacy, defined as patients' perceived ability in obtaining needed information and attention regarding their medical concerns.[40] In a study by Maly and colleagues, perceived self-efficacy was positively associated with nausea resolution in a cohort of low-income women with breast cancer.[41] In any case, it is ultimately the physician's awareness of symptoms that leads to discussion of treatment options with the patient, thereby facilitating symptom resolution. Thus, if minority patients are less likely to mention symptoms for any reason, they may be less likely to receive treatment for their symptoms, which could explain the lower incidence of CINV-related claims for black women in our data. A second potential explanation is that the black women in our sample may differ from white women with respect to unmeasured factors (e.g., body mass index), which could affect the incidence of treatment-induced side effects like CINV.[39, 42, 43] Higher rates of obesity could also lead to chemotherapy under-dosing among black women,[44] which could decrease the incidence of side effects like CINV.

Reporting bias could also occur at the provider level. Our measures of healthcare utilization rely on providers' coding of diagnoses. If providers are less likely to code nausea and related conditions among black patients, for example, due to competing or more pressing health concerns, rates of CINV could appear artificially low in black patients.

We did not observe statistically significant racial differences in patients' receipt of treatment for fatigue or neutropenia, side effects commonly experienced among breast cancer patients including those in our sample. Our lack of observation of a statistically significant relationship between race and fatigue-related services use may be due to our small sample size because estimated risk ratios were consistent with substantial racial variation. Specifically, black patients were 55% less likely than white patients to have claims related to fatigue. Racial differences in use of services related to neutropenia were smaller (10%), however neutropenia is often not symptomatic and thus more commonly diagnosed through routine post-chemotherapy blood testing. Therefore, it is not clear whether neutropenia-related claims capture testing for the condition or patients' experience of neutropenia-related infection.

The positive association between prophylactic NK1 use and CINV-related utilization was also surprising. A possible explanation is that we inadvertently captured claims with associated CINV diagnosis codes used to justify the prophylactic administration of antiemetics. This seems unlikely, however, because our observation window begins the day after chemotherapy initiation and extends for 14 days. Adjuvant chemotherapy regimens for breast cancer should be given no more frequently than every 14 days; thus, we should not have captured claims for antiemetic administration during a women's second cycle of chemotherapy. Therefore, we suspect confounding—specifically confounding by indication—may account for this relationship. For example, patients' (or their providers') level of concern about CINV might help explain why patients who receive NK1s are also more likely to subsequently receive care related to the side effect. Our data suggest that white patients may be more likely to both use NK1s to prevent CINV and be treated for CINV, raising the question of whether black women are not being identified as being in need of CINV prevention and treatment. It is also possible that black women are concentrated within providers or systems where it may be more difficult to access high-quality cancer care,[45] including medications to prevent side effects and services to address them.[45] Black women may also experience access barriers that make both obtaining NK1s and side effect–related care more difficult.

Our study has several limitations. First, we restricted our cohort to fee-for-service Medicare beneficiaries with Part D coverage. It is unknown whether our findings generalize to younger women, Medicare beneficiaries enrolled in an HMO, or women without prescription drug coverage through Part D. Second, we focused on NK1 receptor antagonist use as an indicator of CINV prophylaxis. We did so because NK1s are, according to guidelines, effective only in combination with two other less potent antiemetics (5HT3 antagonists and dexamethasone). However, our measure did include less potent antiemetics without an NK1. It is possible that patients who used an NK1 did not use it in combination with less potent antiemetics. Third, we were unable to account for patients' need for CINV-related care (i.e., their clinical experience with CINV). Fourth, our use of claims data prevented our ability to measure other clinically meaningful outcomes, for example, early termination of or withdrawal from chemotherapy, because it is not possible to determine a woman's intended

chemotherapy regimen or duration. Finally, only 115 black women met our study inclusion criteria, which might have resulted in our lacking statistical power for some comparisons.

These limitations notwithstanding, we present novel data about possible racial variation in receipt of CINV-related care following the first cycle of highly emetogenic adjuvant chemotherapy for early-stage breast cancer. This variation may point to racial differences in women's experience with CINV and their need for its treatment, their preferences for seeking care related to CINV, or their ability to obtain needed care for CINV and potentially other symptoms. Thus, our data suggest that there may be a need for increased awareness and assessment of common side effects during post-treatment visits to ensure patients' supportive care needs are met. Future research should assess whether black women's relatively lower use of CINV-related medications and services is consistent with their informed preferences or whether they may be experiencing barriers to access of needed services. In addition, determining the role of women's side effect experiences in contributing to disparities in important breast outcomes such as patient-reported QOL and treatment adherence represents a novel area for future research.

Table 6. Sample Characteristics, by Race

	White	Black
Number of Patients	1,015	115
Demographic Characteristics (%)		
Age at Cancer Diagnosis		
65-66	20.7	25.2
67-68	24.7	24.4
69-71	25.1	22.6
72-91	29.4	27.8
Marital Status at Diagnosis[a]		
Married/Partnered	52.9	25.2
Non Married/Partnered	42.5	--
Unknown	4.6	--
Median Household Income in Census Tract of Residence[a]		
$0-32,791	21.6	53.0
$32,972-44,039	25.5	--
$44,040-58,436	--	13.0
$58,437-188,340	27.1	--
Unknown	--	0
Proportion of Adult Residents with No High School Degree in Census Tract of Residence[a]		
1.22-9.69%	27.4	--
9.70-16.57%	26.7	--
16.58-27.88%	--	30.4
27.89-75.17%	20.3	57.4
Unknown	--	0
Residence		
Metropolitan County	74.8	82.6
Non-Metropolitan County	25.1	16.4
U.S. Region		
Northeast	19.4	20.0
Midwest	18.0	14.8
West	37.4	14.8
South	25.1	50.4
Clinical Characteristics		
Year of Chemotherapy Initiation[a,b]		
2007	28.9	31.3
2008	20.1	20.9
2009	17.0	18.3
2010	14.8	--
2011	15.4	14.8

2012	3.8	--
Charlson Comorbidity Score[a]		
0	78.4	75.7
1	17.2	--
>1	4.3	--
Cancer Stage		
Stage I	12.8	10.4
Stage II	53.6	56.5
Stage III	33.6	33.0
Hormone Receptor Status[a]		
HR positive	67.0	62.6
HR negative	28.7	--
Unknown	3.7	--
Tumor Grade[a]		
Low	10.3	--
Intermediate	40.1	33.9
High	45.9	56.5
Unknown	4.3	--
Lymph Node Involvement[a]		
Yes	70.9	67.0
No	27.7	--
Unknown	1.4	--
CINV Prophylaxis		
NK1 Receptor Antagonist Use		
Yes	38.7	27.8
No	61.3	72.2

[a] Cells containing proportions that reflect Ns<11 or information that would allow Ns<11 to be derived have been suppressed (--) to protect patients' identities

[b] A small proportion of patients initiated chemotherapy in 2012 because we only have SEER data on patients diagnosed through December 2011. Thus, only patients who received chemotherapy within the first 6 months of 2012 are included in our sample.

Table 7. Unadjusted and Adjusted Associations of Race with Post-Chemotherapy Healthcare Utilization

	Risk and 95% Confidence Intervals				**Risk Ratios and 95% Confidence Intervals, Black v. White**	
	Unadjusted models		Models adjusted for clinical characteristics		Unadjusted models	Models adjusted for clinical characteristics
	White	Black	White	Black		
CINV-Related Utilization						
Any	0.23 (0.21-0.26)	0.15 (0.10-0.23)	0.24 (0.14-0.42)	0.16 (0.08-0.32)	**0.63**[a] **(0.40-0.99)**	0.66 (0.42-1.04)
Outpatient visits	0.23 (0.21-0.26)	0.15 (0.09-0.23)	0.23 (0.13-0.41)	0.15 (0.08-0.311)	**0.64**[a] **(0.41-1.01)**	0.67 (0.43-1.06)
ED visits & inpatient admissions	0.03 (0.02-0.05)	0.03 (0.01-0.09)	N/A[b]	N/A[b]	1.07 (0.39-2.97)	N/A[b]
Any Post-Chemotherapy Utilization	0.91 (0.89-0.93)	0.87 (0.81-0.93)	0.88 (0.80-0.96)	0.84 (0.74-0.94)	0.95 (0.89-1.03)	0.95 (0.89-1.03)
Utilization For Other Side Effects						
Fatigue	0.06 (0.05-0.08)	0.03 (0.01-0.08)	0.02 (0.00-0.09)	0.01 (0.00-0.07)	0.43 (0.14-1.36)	0.45 (0.14-1.44)
Neutropenia	0.41 (0.38-0.44)	0.37 (0.30-0.47)	0.35 (0.24-0.52)	0.32 (0.21-0.50)	0.92 (0.72-1.18)	0.90 (0.71-1.16)

[a] Estimates in bold are marginally statistically significant (p=0.05)

[b] Only unadjusted models for ED visits and inpatients admissions were run due to very low frequency of this outcome, resulting in insufficient cell sizes

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CHAPTER 6. IMPACT OF DRUG FORMULATION CHANGES ON POTENT ANTIEMETIC USE AND DISPARITIES AMONG MEDICARE BENFICIARIES WITH BREAST CANCER

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a major concern for patients beginning cancer treatment.[1] Poorly controlled CINV can have severe physiological consequences, leading to a deterioration of a patient's functional condition and quality of life (QOL).[2–4] Furthermore, uncontrolled CINV can lead to treatment interruptions or withdrawal from potentially beneficial chemotherapy.[4, 5] Therefore, CINV control is critical to high-quality cancer care.

Clinical practice guidelines from oncology professional organizations recommend the use of antiemetic drugs to prevent CINV.[6–8] For several years, the guidelines have recommended prophylactic use of the most potent class of antiemetic, neurokinin-1 receptor antagonists (NK1s), for patients receiving chemotherapy with a high likelihood of CINV. Until 2008, aprepitant, an orally administered NK1 designed to be taken on the first three days of the chemotherapy cycle (i.e., on infusion day and the two subsequent days) was the only NK1 available for CINV prophylaxis. There are several barriers to aprepitant use. Namely, because most private practices and many hospital-based practices do not dispense oral drugs, patients must obtain aprepitant from pharmacies and bring it to their infusion sites on treatment days. Reimbursement rules for Medicare beneficiaries have further complicated access to NK1s because the orally administered drug may be reimbursed under Part B (outpatient medical benefit) or Part D (outpatient prescription drug benefit), which vary in access and cost-sharing requirements. Under Medicare Part B, providers can only write prescriptions for an antiemetic for a single three-day cycle at a time. With Part D plans, patients may encounter prior authorizations and quantity limitations.[9] Moreover, the drug is expensive. Estimates suggest that three aprepitant capsules cost over $500 under Medicare Part D, and patients may be responsible for 25%- to 50% of that cost.[10] Our previous study of breast cancer patients initiating highly emetogenic chemotherapy suggests that barriers to aprepitant use may disproportionately

affect minority patients—we found that black women were 42% less likely than white women to use aprepitant.[11]

In April 2008, the FDA approved fosaprepitant, an intravenous (IV) formulation of aprepitant, for the first of the three daily aprepitant doses. The introduction of fosaprepitant allowed for combined use of the IV and oral formulations by giving providers the option to administer fosaprepitant on day one of the cycle and prescribe oral aprepitant for at-home use on days two and three. In theory, combined IV/oral use was an effective alternative for patients who either failed to obtain aprepitant prior to infusion day or forgot to bring the first aprepitant dose to the clinic on infusion day. In practice, however, controversial coverage decisions by Medicare discouraged combined use of the IV and oral formulations by limiting coverage fosaprepitant on day one to cases where providers could document a patient's previous failure to achieve CINV control with the oral formulation. This may have limited providers' adoption of the IV formulation.[9]

NK1 formulations further evolved in 2010, when a clinical trial demonstrated that a larger, single dose of fosaprepitant could be used as a full replacement for the three-day antiemetic regimen [12]; the FDA approved the new dosage. When administered as full replacements for oral drugs, IV antiemetics may be more convenient for patients because they minimize scheduled medication administration at home. In addition, IV antiemetics may be more affordable for patients. Unlike oral antiemetics, which are sometimes covered by Medicare Part D, IV antiemetics are exclusively covered by Medicare Part B, under which most Medicare beneficiaries have supplemental insurance coverage to assist with their out-of-pocket costs.[13] For these reasons, the approval of single-dose fosaprepitant was expected to decrease the proportion of cancer patients receiving suboptimal CINV prophylaxis. [14]

Analyses of recent data are needed to evaluate the impact of formulation and reimbursement changes on use and disparities in use of NK1s to prevent CINV. Our objective was to assess changes over time in NK1 use among women with early-stage breast cancer, a population that frequently receives highly emetogenic chemotherapy. Because our previous study showed substantial racial disparities in women's NK1 use,[11] we assessed changes in overall and formulation-specific utilization among black and white women over time. We hypothesized that

fosaprepitant availability, particularly the introduction of single-dose fosaprepitant, would lead to increased NK1 use for both black and white patients. We also hypothesized that by providing a more accessible and potentially more affordable alternative to three-day oral aprepitant the introduction of single-dose fosaprepitant may have helped reduce racial disparities in NK1 use.

Methods

Data

We used the National Cancer Institute's Surveillance Epidemiology and End Result (SEER) database linked with Medicare fee-for-service claims from 2006 to 2012. The SEER program consists of population-based cancer registries and represents 28% of the population with cancer. SEER data are merged with fee-for-service Medicare claims to allow for assessments of health services use among Medicare beneficiaries with cancer.[15] Our study was conducted in accordance with a SEER-Medicare data use agreement and was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Sample

We included women aged 65 years and older who were diagnosed with stage I, II, or III breast cancer between January 1, 2007, and December 31, 2011. Eligible women were: (1) not diagnosed at autopsy or death; (2) continuously enrolled in fee-for-service Medicare Parts and A and B for 6 months before and 12 months after diagnosis; and (3) continuously enrolled in Medicare Part D for 12 months after diagnosis. From the 27,160 women meeting these criteria, we restricted our sample to women who received surgery (mastectomy or breast-conserving surgery) and initiated chemotherapy within 6 months of diagnosis (n=4,651). The analysis was further restricted to women whose first cycle of adjuvant chemotherapy included an anthracycline and cyclophosphamide (n=1,569) because guidelines have consistently recommended use of an NK1 for these regimens throughout the study period.[6–8, 16, 17] Because of the small proportion of non-black minorities (n=118), the study was restricted to black and white women (n=1,451). Finally, we restricted our sample to women who initiated chemotherapy between February 1, 2007, and December 31, 2011, to observe Part D claims for antiemetics in the 30 days before chemotherapy initiation and to allow for

12 months of follow-up. These restrictions resulted in a final sample of 1,087 women. A CONSORT diagram is displayed in Figure 3.

Variables

Our outcome was patients' use of an NK1 during the first cycle of highly emetogenic adjuvant chemotherapy (containing an anthracyline and cyclophosphamide). NK1 users were defined as having a Medicare Part D claim for aprepitant (oral formulation), as identified by the drug name, in the 30 days before or on the day of chemotherapy initiation. Alternatively, they had a Part B claim for aprepitant in the 30 days before or on the day of chemotherapy initiation, as identified using Health Care Common Procedure Coding System codes (J8501) and as recorded in the outpatient, physician services, or durable medical equipment claims files. Finally, NK1 users could have a claim for fosaprepitant (IV formulation) (C9242, J1453) on the day of chemotherapy initiation, as recorded in the outpatient or physician services files.

Our exposure of interest was year of adjuvant chemotherapy initiation. Specifically, we were interested in changes in likelihood of NK1 use in 2009, following the FDA's initial approval of fosaprepitant, and in 2011, following the introduction and approval of single-dose fosaprepitant. Patient race (black or white) was measured as reported in the Patient Entitlement and Diagnosis Summary File of SEER-Medicare. Patients' CINV risk is determined primarily by their chemotherapy regimen.[6] Thus our analyses included a small number of covariates related to patients' health status, namely, patient age, comorbidity burden, and cancer stage.

Statistical Analysis

We compared the distributions of patient characteristics between racial groups using chi-squared tests. To directly estimate relative risks with robust error variance, we used modified Poisson regression,[18] estimating changes in NK1 use separately by chemotherapy initiation year. To estimate how changes in NK1 use differed between racial groups, we assessed changes in use of any NK1 and formulation-specific use among black and white patients separately, between 2007 and 2011. We present risks ratios and adjusted risk ratios (aRR) with 95% confidence intervals (CI) for NK1 use.

Consistent with the IOM's approach to measuring healthcare disparities, which recognizes the mediating role of an individual's socioeconomic status (SES) and related factors, our models did not attempt to adjust for SES because doing so may reduce or eliminate the estimated independent effect of race on care, giving a false picture of the experience of vulnerable patients.[19] Moreover, SEER-Medicare includes only area-level measures of socioeconomic status (SES) (e.g., census tract–level median income), which may misclassify individuals' SES, particularly for minorities.[20, 21]

Sensitivity Analysis

To account for women's potential previous experience with chemotherapy and CINV, our primary analysis was limited to women whose first cycle of chemotherapy included an anthracycline and cyclophosphamide. In sensitivity analysis we expanded the cohort to women initiating their first anthracycline and cyclophosphamide containing cycle without requiring this treatment to be the first chemotherapy received (N=1,176). Results from this sensitivity analysis were consistent with the primary analysis and are not shown.

Results

Our sample included 976 white women and 111 black women. There were no racial differences in health or tumor-related characteristics (Table 8). Compared to white women, black women were 10% less likely to use any NK1 over the study period (p=0.03) and 11% less likely to use aprepitant (p=0.01). There were no statistically significant differences by race in overall fosaprepitant use (Table 8).

Models adjusted for health characteristics also show NK1 use increasing over time for both white and black patients (Table 8). Patients of both racial groups were more than twice as likely to use an NK1 in 2011 compared to 2007 (aRR for white patients: 2.67, 95% CI: 2.13-3.35; aRR for black patients: 2.54, 95% CI: 1.03-6.25). However, racial gaps have persisted. In 2007, the likelihood of NK1 use was 0.24 for white patients and 0.13 for black patients; increasing to 0.64 and 0.32 for white and black patients, respectively, by 2011 (Table 9). For each individual year, racial differences in likelihood of NK1 use were large but not statistically significant (Figure 3).

Among white patients, the likelihood of NK1 use increased by 11% between 2008 and 2009 and by 23% between 2010 and 2011. Aprepitant use specifically increased from 0.20 to 0.28 between

2007 and 2010. The proportion of white patients using NK1s continued to increase between 2010 and 2011, driven by an increase in the likelihood of fosaprepitant use from 0.20 to 0.44, while aprepitant use fell (Table 9).

Among black patients, use of NK1s increased by 8% between 2008 and 2009 and between 2010 and 2011 (see Table 9). For black patients, the formulation-specific models did not show statistically significant changes in likelihood of aprepitant or fosaprepitant use over time. Descriptively, black patients' increasing likelihood of fosaprepitant use, which rose from 0.09 in 2009 to 0.31 in 2011, appears to explain the increase in any NK1 use over time for black patients because aprepitant use did not increase over time for this group (see Table 9).

Discussion

Changes in the formulation of and reimbursement for fosaprepitant had the potential to increase NK1 use for both black and white patients as well as to reduce racial disparities in NK1 use. Specifically, with the availability of a more accessible and affordable alternative to three-day oral aprepitant, we hypothesized that: (1) overall use of NK1 would increase and (2) disparities in NK1 use by patients who may experience cost or access barriers to prescription medication use (e.g., minority patients) would decrease.[22–24] In our sample of Medicare beneficiaries initiating highly emetogenic chemotherapy for early-stage breast cancer, NK1 use increased substantially for both black and white patients between its initial approval in 2008 and 2011. This increase suggests that, particularly after single-dose fosaprepitant was introduced in 2010 as an alternative to three-day aprepitant, providers recognized the IV drug as a more convenient option for all patients.[9] That NK1 use has improved for all patients in our sample is encouraging and suggests that over time more patients are receiving adequate prevention of CINV. However, the observed persistent racial gap indicates that the CINV prevention needs of many black women are not being met. Thus, targeted efforts to increase NK1 use among black patients may be needed.

To inform interventions to reduce these disparities, future research should assess the contribution of provider- versus patient-level barriers to NK1 use. For example, black women may be more likely to receive care within lower-performing systems[25] where providers do not routinely prescribe NK1s in accordance with clinical guidelines[26] either because the systems' antiemetic

order sets do not align with guidelines or individual prescribers are unfamiliar with the guidelines.[27] Second, black women and white women may be equally likely to be prescribed an NK1, but black women may be less likely to fill a prescription for aprepitant due to financial[22] or other access barriers.[23, 24] In our previous SEER-Medicare study of racial disparities in antiemetic use among breast cancer patients, disparities in any NK1 and aprepitant use appeared to be partly explained by SES differences between black and white women.[11] These SES differences could translate into differential access to high-quality providers and/or differential ability to access pharmacies[23, 24] and to afford expensive prescription drugs.[22]

One previous analysis of cancer care quality indicators within the Veterans Affairs (VA) system concluded that hospital-level variation fully explained racial disparities in guideline-concordant use of 5HT3 receptor antagonists for CINV prophylaxis.[26] However, the primary role of hospital-level variation in explaining disparities in antiemetic use could be unique to the VA system, which offers more comprehensive drug coverage than any other public or private payer in the United States, potentially obviating patient-level cost barriers to oral antiemetic use.[28] Future studies of cancer patients in the general population should investigate the role of site of care in explaining disparities in antiemetic use. If disparities appear to reflect differential prescribing by site of care, provider- or system-level interventions may be appropriate. Previous research has demonstrated that several institution-wide strategies, including adoption of institutional guidelines[29–31] and implementation of guidelines through use of physician audit and feedback,[30, 31] opinion leaders, and preprinted antiemetic orders[31] may be effective strategies for improving providers' antiemetic prescribing.

Understanding patient-level contributors to disparities will require data about both providers' prescribing and patients' receipt of NK1s. If black and white patients are equally likely to be prescribed an NK1 but black patients are less likely to fill aprepitant prescriptions, patient-level barriers must be targeted to reduce persistent disparities in NK1 use. For example, if disparities in NK1 use result from patients' differential ability to afford aprepitant,[22, 32] interventions might encourage conversations between oncologists and patients regarding affordability of prescription medications.[22] These conversations may help identify patients who are in need of financial assistance for medical and prescription drug costs. Alternatively, knowledge that patients lack

convenient transportation to a pharmacy[23, 24] could inform decisions about prescribing oral versus intravenous antiemetics.

To our knowledge, no studies to date have specifically assessed patients' preferences for IV compared to oral antiemetic regimens.[14] However, results from a handful of studies suggest that efforts to facilitate the prescription of IV antiemetics may address patients' perceived barriers to achieving adequate prevention of CINV. Specifically, a survey of patients and providers concerning communication about CINV showed that patients were twice as likely as providers to report trying to limit the number of medications taken to prevent CINV, suggesting that patients may prefer simpler regimens.[33] Moreover, in a discrete choice experiment assessing patients' willingness to pay to prevent CINV, the authors concluded that cost contributed more to patients' choices about avoiding CINV than any other single attribute This suggests that the cost of medications to prevent CINV may affect patients' likelihood of using them.[34] The prescription of IV antiemetics, including single-dose fosparepitant, would appear to be consistent with available evidence on patients' preferences surrounding antiemetic formulations. In addition to simplifying regimens and minimizing scheduled medication administration at home, IV antiemetics are typically covered under Medicare Part B (versus Part D); thus, they may be more affordable for the large majority of Medicare beneficiaries who have supplemental insurance coverage to assist with their out-of-pocket Part B costs.[13]

Our study has a number of limitations. First, we were unable to account for site-level variation in care; neither could we separate physicians' failure to prescribe aprepitant from patients not filling prescription. Second, we focused on fee-for-service Medicare beneficiaries with Part D coverage. It is unknown whether our findings generalize to younger women, Medicare beneficiaries enrolled in Medicare Advantage plans, or women without prescription drug coverage through Part D. Third, only 111 black women met our study inclusion criteria, which might have resulted in our lacking statistical power for some comparisons, particularly in the formulation-specific models. Finally, our data allowed us to examine NK1 use through 2011, only one year after the introduction and FDA approval of single-dose fosaprepitant. Studies using more current data would be needed to examine longer-term effects on overall NK1 use and, ultimately, improvements in CIV prophylaxis.

Our findings demonstrate that NK1 use has improved over time for black and white patients following the introduction of IV fosaprepitant and the potentially more convenient and affordable alternative to oral aprepitant. This trend is encouraging and suggests that, over time, more patients are receiving adequate prevention of CINV in accordance with clinical practice guidelines. However, substantial racial gaps in NK1 use remain, indicating that the CINV prevention needs of many black women are not being met. Given patients' preferences for simpler and less expensive antiemetic regimens, strategies that facilitate providers' prescription of IV antiemetics, including fosaprepitant as a substitute for three-day oral aprepitant, may improve overall rates of guideline-concordant CINV prophylaxis, particularly for patients who have difficulty accessing or adhering to more complex oral regimens.

Table 8. Aim 3 Sample Characteristics, by Race

	White	Black	p-value
Number of Patients	976	111	
Characteristics (%)			
Age at Cancer Diagnosis			
65-66	20.5	25.3	0.80
67-68	24.7	24.3	
69-71	25.3	22.5	
72-91	29.5	28.8	
Year of Chemotherapy Initiation			
2007	30.0	32.4	0.90
2008	20.9	21.6	
2009	17.7	18.9	
2010	15.3	11.7	
2011	16.0	15.3	
Charlson Comorbidity Score			
0	78.6	76.6	0.20
1	17.1	--	
>1	4.3	--	
Cancer Stage			
Stage I	13.1	10.8	0.80
Stage II	53.4	55.9	
Stage III	33.5	33.3	
Hormone Receptor Status			
HR positive	66.9	63.1	0.60

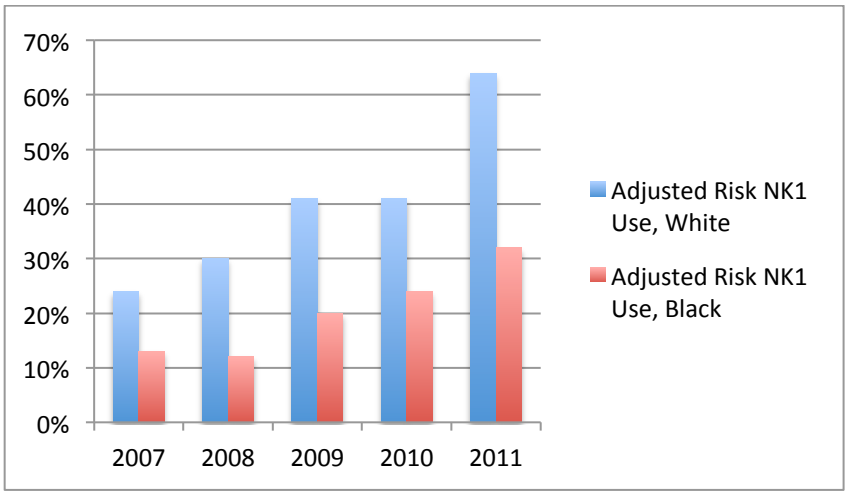
HR negative	28.6	--	
Unknown	4.5	--	
Tumor Grade			0.09
Low	10.5	--	
Intermediate	40.4	33.3	
High	45.7	56.8	
Unknown	3.5	--	
Lymph Node Involvement			
Yes	71.1	66.7	0.62
No	27.6	--	
Unknown	1.3	--	
Overall NK1 Use			
Any NK1, % Yes	37.2	27.0	**0.03**
Aprepitant, % Yes	27.3	16.2	**0.01**
Fosaprepitant, % Yes	13.2	10.9	0.47

Cells including percentages reflecting Ns<11 or information that would allow Ns<11 to be derived were suppressed to protect patients' identities.
Patients with "unknown" values for hormone receptor status, tumor grade, and lymph node involvement not included in p-value calculations.

Table 9. Adjusted NK1 Use Over Time, Overall and by Formulation, Among Black and White Patients

	White			Black		
Any NK1 Use	Risk	aRR	95% CI	Risk	aRR	95% CI
2007	0.24	REF	REF	0.13	REF	REF
2008 (Initial FDA Approval)	0.30	1.25	0.94-1.65	0.12	0.96	0.31-2.99
2009	0.41	**1.70**	**1.31-2.21**	0.20	1.57	0.58-4.22
2010 (Single Dose Introduced)	0.41	**1.73**	**1.32-2.25**	0.24	1.95	0.66-5.73
2011	0.64	**2.67**	**2.13-3.35**	0.32	**2.54**	**1.03-6.25**
Aprepitant Use						
2007	0.20	REF	REF	0.14	REF	REF
2008	0.25	1.23	0.93-1.63	0.08	0.64	0.18-2.35
2009	0.26	1.29	0.96-1.73	0.12	0.91	0.30-2.79
2010	0.28	**1.36**	**1.01-1.82**	0.05	0.40	0.05-3.09
2011	0.21	1.05	0.76-1.46	0.14	1.00	0.32-3.14
Fosaprepitant Use						
2009	0.17	REF	REF	0.09	REF	REF
2010	0.20	1.14	0.73-1.80	0.29	3.03	0.67-13.90
2011	0.44	**2.53**	1.75-3.65	0.31	3.26	0.67-15.91

Throughout the study period, 363 white women and 30 black women used any NK1; 266 white women and 18 black women used aprepitant; 129 white women and 12 black women used fosaprepitant.
Any NK1 and aprepitant models controlled for age, comorbidity, and cancer stage. Fosaprepitant models controlled only for age due to insufficient cell sizes.
Estimates in bold are statistically significant at the $p<0.05$ level.



Differences are not statistically significant at the p<0.05-level.

Figure 3. Racial variation in NK1 use over time.

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CHAPTER 7. DISCUSSION

Conclusions

Race and NK1 Use

Findings from this study provide evidence about the quality of CINV prophylaxis among black and white breast cancer patients beginning highly emetogenic adjuvant chemotherapy. We observed substantial racial disparities in guideline-recommended use of NK1s for CINV prophylaxis: Black women were 32% less likely than white women to use any NK1 and 46% less likely to use oral aprepitant specifically. We offer two main hypotheses as to why aprepitant may be underused by black women.

First, black women may be equally as likely as white women to be prescribed aprepitant but less likely to fill their prescriptions, possibly due to financial or other access barriers.[22] Second, black women may be more likely to see providers who do not prescribe NK1s in accordance with clinical guidelines because they are more likely to be treated in lower-performing settings.[25, 26] Both explanations seem plausible given our findings. Specifically, the fact that disparities in NK1 and aprepitant use were somewhat attenuated when socioeconomic status (SES)-related factors were added to the models suggests that the disparities are at least partly explained by SES differences between black and white women. These SES differences could translate into differential ability to pay for prescription drugs or differential access to high-quality care (including guideline-adherent antiemetic prescribing). Our identification of racial disparities in oral but not intravenous NK1 use supports the hypothesis that fosaprepitant is more affordable for and more easily accessed by patients.

Racial Variation in Post-Chemotherapy Healthcare Utilization for CINV

We found that black women were less likely to receive CINV-related care in the post-chemotherapy period. This finding was counter to our hypothesis that black women would be more likely to experience CINV-related utilization because of evidence of their underuse of NK1s for CINV

prophylaxis. Instead, in this SEER-Medicare sample, black women were at lower risk for both using an NK1 and for receiving treatment for CINV. Although the racial difference in CINV-related utilization was not statistically significant after adjustment for covariates, estimates were still consistent with lower utilization among black patients. We observed no racial variation in the use of any outpatient services during the 14 days following chemotherapy initiation. Thus, it seems unlikely that racial differences in general access or care-seeking behavior fully explain racial variation in CINV-related services use.

It may be that the variation we observed is specific to CINV or symptom management. There are two reasons black women may be less likely to have claims with diagnosis codes related to CINV. First, black and white women may be at equal risk of experiencing CINV but black women may be less likely to report this experience to their providers.[35] A second potential explanation is that the black women in our sample may differ from white women with respect to unmeasured factors (e.g., body mass index), which could affect the incidence of treatment-induced side effects like CINV.[36–38] Reporting bias could also occur at the provider level. Our measures of healthcare utilization rely on providers' coding of diagnoses. If providers are less likely to code nausea and related conditions among black patients, for example, due to competing or more pressing health concerns, rates of CINV could appear artificially low in black patients.

The positive association between prophylactic NK1 use and CINV-related utilization was also surprising. We suspect confounding—specifically confounding by indication—may account for this relationship. For example, patients' (or their providers') level of concern about CINV might help explain why patients who receive NK1s are also more likely to subsequently receive care related to the side effect. Our data suggest that white patients may be more likely to both use NK1s to prevent CINV and be treated for CINV, raising the question of whether black women are not being identified as being in need of CINV prevention and treatment. It is also possible that black women are concentrated within providers or systems where it may be more difficult to access high-quality cancer care,[25] including medications to prevent side effects and services to address them. Black women may also experience access barriers that make both obtaining NK1s and side effect–related care more difficult.

Changes in NK1 Use and Disparities over Time

In our sample, fosaprepitant use increased substantially for both black and white patients between its initial approval in 2008 and the end of our study period in 2011. This increase suggests that, particularly after single-dose fosaprepitant was introduced in 2010 as an alternative to three-day aprepitant, providers recognized the IV drug as a more convenient option for all patients. That NK1 use has improved for all patients in our sample is encouraging and suggests that over time more patients are receiving adequate prevention of CINV. However, the persistent racial gap that we observed indicates that the CINV prevention needs of many black women are not being met. Thus, targeted efforts to increase NK1 use among black patients may be needed.

To inform these efforts, future research should assess the contribution of provider versus patient-level barriers to use. For example, black women may be more likely to receive care within lower-performing systems[25] where providers do not routinely prescribe NK1s in accordance with clinical guidelines either because the systems' antiemetic order sets do not align with guidelines or individual prescribers are unfamiliar with the guidelines.[27] Previous research has demonstrated that several institution-wide strategies, including development of institutional guidelines[29–31] and implementation of guidelines through use of physician audit and feedback,[30, 31] opinion leaders, and preprinted antiemetic orders[31] may be effective strategies for improving providers' antiemetic prescribing.

Alternatively, if black and white patients are equally likely to be prescribed an NK1 but black patients are less likely to fill aprepitant prescriptions, patient-level barriers are likely to contribute to persistent disparities in NK1 use. In particular, disparities in use may be partly explained by patients' differential ability to afford aprepitant[22, 32] or differential access to a pharmacy, for example, due to lack of convenient transportation.[23, 24] Interventions to address patient-level barriers to aprepitant use might encourage conversations between oncologists and patients regarding access to and affordability of prescription medications.[22] These conversations may help identify patients who are in need of financial assistance for medical and prescription drug costs. Providers' knowledge of patients' difficulty with pharmacy access or medication costs could also inform decisions about prescribing oral versus intravenous antiemetics for all patients.

Clinical and Policy Implications

We observed persistent racial disparities in use of NK1s to prevent CINV among Medicare beneficiaries initiating highly emetogenic chemotherapy for early-stage breast cancer. Although, in our sample, disparities in NK1 use did not appear to contribute to disparities in women's CINV-related services use as captured by Medicare administrative claims, disparities in CINV prophylaxis are nonetheless concerning if they contribute to disparities in quality of life (QOL) or women's adherence to chemotherapy schedules. Future research should assess the contribution of disparities in quality of side effect management to disparities in the latter two outcomes. In addition, before developing interventions to address disparities in quality of CINV prophylaxis, future studies should seek to elucidate the underlying causes of disparities. Namely, keys to better understanding the source of disparities will lie in examining the relative roles of patient-level factors (i.e., financial and other access barriers) and provider-level factors (i.e., variable prescribing at the provider or practice level). To the extent that patient-level factors explain disparities in CINV prophylaxis, the results of our study together with prior research exploring patients' perspectives on antiemetic use[33, 34] suggest that policies and strategies that facilitate providers' prescription of IV antiemetics, including fosaprepitant as a substitute for three-day oral aprepitant, may improve overall rates of guideline-concordant CINV prophylaxis. This may be particularly true for patients who have difficulty accessing or adhering to more complex oral regimens,[9] including racial minority and low-income patients.

Limitations

This section addresses limitations of the current study, and offers recommendations for future studies that address these shortcomings. One limitation of our study concerns the generalizability of our findings. We focused on fee-for-service Medicare beneficiaries with Medicare Part D coverage. It is unknown whether our findings generalize to younger women with early-stage breast cancer, Medicare beneficiaries enrolled in an HMO, or women without prescription drug coverage through

Part D. Additionally, because of the limited number of minority women represented in SEER, we may have lacked statistical power for some comparisons. This is particularly true of the fosaprepitant models, which were limited to women who initiated chemotherapy in 2009 or later. Future studies could attempt to replicate our findings in samples of breast cancer patients who are more diverse with respect to race and ethnicity, age, and insurance status.

Additional limitations relate to the use of Medicare administrative claims data. First, we could not separate physicians' failure to prescribe aprepitant from patients not filling prescriptions. Thus, although we have documented the existence of disparities, we are unable to identify the underlying causes of the observed disparities using SEER-Medicare data. Future studies should attempt to use clinical data to ascertain whether the disparities identified here reflect disparities in aprepitant prescriptions or fills. If black and white women are equally likely to be prescribed NK1s but black women are less likely to fill these prescriptions, disparities may in fact reflect barriers related to affordability and accessibility. If black women are less likely to be prescribed aprepitant, disparities may reflect provider-level factors. Namely, black women may be more likely to see providers who do not prescribe NK1s in accordance with clinical practice guidelines or providers may be less likely to prescribe aprepitant to patients who are minorities or low-income due to perceptions about patients' likelihood of filling prescriptions or complying with the dosing regimen. Second, we may have under-captured NK1 use overall, particularly in situations where the oral medication was provided in clinic and not billed to Medicare. However, we do not believe that capture issues would differentially affect black versus white patients, so comparisons between groups should be valid nonetheless.

Third, our use of claims data prevented our ability to measure several clinically meaningful outcomes in Aim 2. In addition to assessing women's post-chemotherapy healthcare utilization, including their use of services related to CINV, we would have ideally also assessed their early termination of or withdrawal from chemotherapy as well as extended gaps between chemotherapy cycles. Using SEER-Medicare, we were unable to reliably determine a woman's intended chemotherapy regimen or duration, making it infeasible to recognize unintended interruptions or termination of treatment that could potentially occur due to uncontrolled side effects. Studies using clinical data may be able to more accurately define a woman's intended treatment regimen and

deviations from it. Because adherence to the chemotherapy schedule is an important determinant of its effectiveness, it is a very important outcome for future research on breast cancer disparities and consequences of uncontrolled side effects.

Future Directions

Understanding how treatment-induced side effect management influences racial disparities in care and outcomes for patients with breast and other cancers will be imperative for informing interventions that target modifiable factors to reduce disparities. The results of this dissertation provide a foundation for future research that:

1. Uses clinical data to assess the relationship between breast cancer patients' NK1 use and their likelihood of experiencing delays in or early termination of adjuvant chemotherapy;
2. Explores patients' perceptions about potential barriers to taking oral antiemetics (including aprepitant) for the prevention of CINV and their preferences for oral versus intravenous drugs;
3. Explores providers' perceptions about potential barriers to guideline-adherent antiemetic prescribing and use;
4. Assesses disparities in the prophylactic use of other supportive cancer therapies (e.g., growth factors) and the impact on disparities in chemotherapy use and outcomes; and
5. Informs interventions to maximize appropriate use of supportive cancer therapies, including antiemetics to prevent CINV.

In addition, several specific research studies would directly extend the results of this dissertation by helping elucidate the sources of disparities in NK1 use. For example, natural extensions of this study could use data on patients with diverse cancers within a health system or group of health systems to: (1) assess variation in patients' receipt of prescriptions for aprepitant versus disparities in their filling of aprepitant prescriptions; (2) if variation exists at the prescriber level, assess the effects of provider or practice characteristics on under-prescription; (3) if variation exists at the patient level (i.e., prescription fills), assess the role of individual-level measures of SES on under-filling. Moreover, access to more recent data (i.e., 2011–2016) would allow for an updated

assessment of the effect of antiemetic formulation changes on use of the drugs and the current extent of disparities in use to inform the scope of the problem and potential interventions to increase guideline-concordant antiemetic prescribing and use, particularly for low-access groups.

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