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Appropriate Use of Antiemetics to Prevent Chemotherapy-Induced Nausea and Vomiting

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Overuse of low-value oncology services has received increasing attention recently.[1] National campaigns such as “Choosing Wisely” have prompted medical specialty societies to identify areas for reducing low-value utilization. The use of antiemetic drugs to prevent chemotherapy-induced nausea and vomiting (CINV) exemplifies an area with high potential for overuse, and was targeted in the American Society of Clinical Oncology (ASCO)’s 2013 set of Choosing Wisely recommendations.[2] Specifically, providers were cautioned not to use potent antiemetics (i.e., neurokinin-1 receptor antagonists [NK1-RAs]), which are intended for use among patients receiving chemotherapy with a high risk of CINV, for patients initiating chemotherapy with a low or moderate risk of CINV.[2]

The past two decades have seen substantial advances in the development of antiemetic drugs. Namely, 5-hydroxytyptamine receptor antagonists (5HT3-RAs) and NK1-RAs have widened tolerability of potentially beneficial chemotherapy regimens with a moderate to high emetogenic risk. However, these advances have come at a price. In addition to their substantial cost to patients and the healthcare system, when used unnecessarily, i.e., with minimal to low risk chemotherapy, potent antiemetic agents may expose patients to excess toxicity.[3]

For several years, oncology professional organizations, including ASCO, have produced and endorsed clinical practice guidelines specifying appropriate use of antiemetics.[4] However, guideline adherent use has been shown to be suboptimal.[5] While overuse of antiemetics among patients taking chemotherapy drugs with lower CINV risk is concerning because of the potential for excess cost and toxicity, underuse can impact patients’ quality of life (QOL)[6] and their adherence to prescribed chemotherapy regimens.[7] Even so, underuse is well documented. For example, in a study of Texas Medicare beneficiaries with lung cancer initiating platinum-based chemotherapy regimens between 2001–2007, only 10% of patients received NK1-RAs after their inclusion in guidelines in 2006. Rates of use of long-recommended 5HT3-RAs and steroids were also low, at around 80% and 65%, respectively.[8] In addition, an analysis of women with early-stage breast cancer beginning adjuvant chemotherapy containing an anthracycline and cyclophosphamide between 2006–2012 revealed that only 40% of women received an NK1-RA in accordance with guideline recommendations.[9]

In the current issue of *JAMA Oncology*, Encinosa and Davidoff present valuable data about the potential overuse of antiemetics.[10] In their large observational, claims-based study of

privately insured patients with cancer initiating chemotherapy between 2008–2015, the authors examined overuse relative to recent guidelines, and associated expenditures. In particular, they were interested to learn whether overuse declined with the release of the 2013 ASCO Choosing Wisely recommendation. The authors observed substantial overuse in the pre-Choosing Wisely period, including overuse among patients beginning a chemotherapy regimen with a minimal emetogenic risk, where no prophylaxis is recommended. Specifically, in the minimal and low risk settings, 15% and 20% of patients received stronger antiemetic therapy than recommended. Among patients beginning moderate or high-risk chemotherapy regimens, who were represented as a single group in this study, 32% appeared to preemptively fill prescriptions for drugs typically reserved for breakthrough symptoms several days after chemotherapy. The largest difference in spending between a guideline-consistent antiemetic regimen and an antiemetic regimen with overuse was observed for the intravenous low CINV risk chemotherapeutic agents: $452 or 587%.

This paper suggests that the Choosing Wisely recommendation had a limited impact on overuse. In the six months following the CW announcement, overuse declined for all intravenous chemotherapy, but not for orally- administered chemotherapy. The decline was short-lived, however. Following this initial six-month period, overuse climbed again in all chemotherapy groups except for the low-risk intravenous chemotherapy group.

Given the existence of clear guidelines concerning antiemetic use for CINV prophylaxis, why is inappropriate use persistent? As suggested by the authors, insurer practices may play a role. Currently, Medicare covers the three-drug oral regimen of an NK1-RA, 5HT3-RA, and a steroid not only for highly emetogenic chemotherapy regimens, for which guidelines suggest all three drugs are necessary to achieve sufficient CINV prophlyaxis, but also for moderately emetogenic chemotherapy regimens.[11] Not only do guidelines not recommend the addition of an NK1-RA for patients beginning moderately emetogenic chemotherapy, but the 2013 ASCO Choosing Wisely recommendation specifically defines use of NK1s in this setting as low-value, cautioning against the practice. Given the influence of Centers for Medicare and Medicaid (CMS) coverage decisions on those of private insurers, this policy may drive overuse of NK1-RAs in the moderate risk setting, not only among Medicare beneficiaries, but also among the privately insured.

Another likely source of inappropriate use of antiemetics may occur at the prescriber level. Non guideline-adherent prescribing might be driven by individual provider-level factors, for example, a lack of awareness of or familiarity with guidelines, lack of agreement with guidelines, or inertia of previous practice.[12] It might also reflect institutional policies, or lack thereof, surrounding antiemetic prescribing practices, for example, an institution’s failure to include appropriate regimens in the antiemetic order sets for specific chemotherapy regimens.

The appropriate use of antiemetics for CINV prophylaxis is a critical aspect of high-quality cancer care. Underuse of recommended antiemetic drugs may result in uncontrolled CINV, which can have implications for patients’ QOL and their ability to continue potentially beneficial chemotherapy. On the other hand, the overuse of antiemetics in settings where they are not recommended may results in excess cost and toxicity. The release of the 2013

ASCO Choosing Wisely recommendation is an important first step toward addressing potentially low-value use of antiemetics. However, as demonstrated in this and other analyses, guidelines and Choosing Wisely recommendations in isolation are not sufficient to alter practice patterns. Rather, dissemination and implementation initiatives connected to these recommendations are vital to success. In the case of antiemetic use, there are several vehicles through which inappropriate use could be reduced, if successfully leveraged:

1. **CMS could revise its antiemetic coverage policy to more closely align with clinical practice guideline recommendations regarding appropriate use.** In particular, this may help to mitigate potential overuse of NK1-RAs during the first cycle of a moderately emetogenic chemotherapy regimen.

2. **Insurers could adopt innovative coverage designs to encourage appropriate use.** In particular, CMS and commercial insurers might consider value-based design where antiemetic cost sharing for patients is lower in high-value setting (i.e., among patients starting chemotherapy regimens with a high risk of CINV), and higher in low-value settings (i.e., among patients starting regimens with a minimal risk of CINV).

3. **Institutions could adopt and implement clear policies governing antiemetic prescribing.** Several older models exist. For example, in 1998, Memorial Sloan Kettering developed institutional guidelines in an effort to avoid overuse of then newly available and expensive 5HT3-RAs. The guidelines were implemented through use of pre-printed antimeteic order forms for each emetic category of chemotherapy. Nurses and pharmacists reviewed physicians' antiemetic orders, and contacted physicians who were not in compliance. An evaluation of the strategy found that it optimized prescribing and reduced costs, without jeopardizing patients' outcomes.[13] In addition to developing and disseminating institutional guidelines, in 2003, Baystate Regional Cancer Program provided feedback to providers not only about non-compliance but also regarding patients who experienced uncontrolled CINV as a result, resulting in increased compliance.[14] Today, the wide availability of clear, regularly updated guidelines and increasing utility of electronic health record (EHR) software can facilitate institutional strategies to increase appropriate prescribing. In particular, medication order entry templates and feedback through the EHR have proven to be effective mechanisms for aligning prescriber practices with guidelines.[15] In considering how best to leverage the EHR to guide appropriate antiemetic prescribing, it will be important to consider the potential limitations, for example, the risk of provider fatigue with interruptive alerts of non-compliance.

4. **Appropriate use of antiemetics should be included in quality metrics.** For example, the ASCO Quality Oncology Practice Initiative (QOPI) -- a practice-based quality assessment program -- is a launching a measure corresponding to the 2013 ASCO Choosing Wisely recommendation this fall. Specifically, the QOPI measure will allow practices to assess the proportion of patients on cycle 1 of chemotherapy with a low or moderate emetogenic risk who are receiving an NK1-RA. QOPI and similar groups might consider an additional measure of

underuse of NK1-RAs among patients receiving chemotherapy with high emetogenic risk.

In summary, Encinosa and Davidoff have presented compelling evidence of antiemetic overuse and the limited effectiveness of a Choosing Wisely recommendation alone in reducing overuse. Nonetheless, ASCO's identification of antiemetic overuse as a common low-value practice is a key step toward increasing awareness of antiemetic prescribing guidelines, and enabling implementation efforts. Moving forward, additional strategies and research are needed to facilitate appropriate use by both patients and providers.

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