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Prescription of Prophylactic Antiemetic Drugs for Patients Receiving Chemotherapy With Minimal and Low Emetic Risk

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IMPORTANCE The use of antiemetic drugs for patients receiving chemotherapy with low or minimal emetic risk has been recognized as a growing concern for health care costs and patients' welfare. Relatively few studies have examined antiemetic prophylaxis or treatment of emesis associated with chemotherapy with lower emetic risk.

OBJECTIVE To describe the pattern in Japan of overprescribing prophylactic antiemetic drugs to patients who have received intravenous chemotherapy with minimal or low emetic risk.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of a health insurance claims database linked with the hospital-based cancer registry of 122 designated cancer care hospitals covered the period from September 1, 2010, to December 31, 2012. Data were included from patients who (1) were diagnosed with breast, lung, colorectal, stomach, cervical, or prostate cancer; (2) were 20 years or older at the time of the diagnosis; and (3) received intravenous chemotherapy with minimal or low emetic risk. The data from patients with advanced stage cancer (stage IV) were excluded. Data were analyzed from March 20, 2014, to June 30, 2016.

MAIN OUTCOMES AND MEASURES The percentage of chemotherapy administration involving patients prescribed prophylactic antiemetic drugs, namely, a neurokinin 1 receptor antagonist, serotonin receptor antagonist, and/or dexamethasone, was calculated. The costs of potentially unnecessary antiemetic drugs were estimated using the National Health Insurance drug price list for 2011.

RESULTS A total of 8545 patients (5886 women [68.9%] and 2659 men [31.1%]; mean [SD] age, 61.9 [12.8] years) undergoing 73 577 administrations of chemotherapy with minimal emetic risk (2464 patients; 22 619 administrations) or low emetic risk (6081 patients; 50 958 administrations) were identified. Of these, patients who received 24 373 administrations of chemotherapy with a low emetic risk (47.8%) and 633 administrations of chemotherapy with a minimal emetic risk (2.8%) were prescribed serotonin receptor antagonists and dexamethasone. Outpatients in the low emetic risk group underwent more frequent administration of chemotherapy that included prescription of both drugs (53.1% of the chemotherapy; 95% CI, 51.6%-54.7%) compared with inpatients (33.7% of the chemotherapy; 95% CI, 31.7%-35.9%). Consequently, approximately ¥170 million (US $1.6 million) was unnecessarily spent on prophylactic antiemetic drugs for these patients.

CONCLUSIONS AND RELEVANCE A substantial number of patients receiving chemotherapy with minimal and low emetic risk were prescribed potentially unnecessary prophylactic antiemetic drugs. The judicious use of these drugs could spare the burden of extra costs and the potential risk for adverse effects for patients.

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Supplemental content

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Chemotherapy-induced nausea and vomiting (CINV) is a major concern for patients who receive chemotherapy. Studies have pointed out that patients receiving chemotherapy reported that CINV was one of their most concerning adverse effects.[1,2] Unfortunately, CINV often predisposes patients to not comply with treatment regimens and imposes mental and physical burdens that diminish their quality of life.[3-5] Recently, more effective and better-tolerated antiemetic agents have become available.[6] Clinical practice guidelines have incorporated these drugs to prevent CINV.[7,8]

Despite widespread concern, not all chemotherapeutic drugs cause severe CINV. Chemotherapeutic drugs are classified according to their documented emetogenicity.[7-9] Specifically, drugs that cause acute CINV more than 90% of the time, 30% to 90% of the time, 10% to less than 30% of the time, and less than 10% of the time are classified as high, moderate, low, and minimal emetic risk, respectively.[9] The antiemetic guidelines of the American Society of Clinical Oncology[7] and Japanese Society of Clinical Oncology[8] recommend single-agent therapy with dexamethasone for patients receiving chemotherapy with low emetic risk for the acute-phase CINV, whereas the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology[10] recommend single-agent therapy with dexamethasone, a serotonin receptor antagonist, or a dopamine receptor antagonist. These organizations have slight differences in their recommended prophylactic antiemetic drugs for patients at low emetic risk.[11] All 3 guidelines recommend no prophylactic drugs for patients receiving chemotherapy with minimal emetic risk. Moreover, the antiemetic guidelines explain that CINV in the delayed phase is not a major problem for patients undergoing chemotherapy with low or minimal emetic risk.[8]

Adherence to the antiemetic guidelines has been repeatedly reported to be suboptimal in community practices.[12-18] Few studies have reported the patterns of prescribing antiemetic drugs for lower emetic risk groups. In a single-facility study,[14] adherence to guidelines in the low emetic potential group was only 11% because the remaining patients received a serotonin receptor antagonist in addition to corticosteroids. However, serotonin receptor antagonists, including the second-generation granisetron hydrochloride, have been proven to provide little benefit as primary prophylaxis in patients receiving chemotherapy with a low emetic risk.[19] Unfortunately, few clinical trials of antiemetic prophylaxis or treatment of emesis associated with these drugs with low emetic risks have been published.[20] This lack may lead to overtreatment with antiemetic drugs for patients at lower risk.

The overuse of health care services has recently gained increasing public attention owing to rising health care expenditures worldwide.[21-23] Responding to the Choosing Wisely campaign by the American Board of Internal Medicine Foundation, the American Society of Clinical Oncology listed the use of antiemetic drugs targeting chemotherapy with high emetic risk for chemotherapy with low or minimal emetic risk as one of "the things that patients and doctors should question."[24(p1)] Despite the growing concern, to our knowledge, only the single small-scale study[14] mentioned above has examined the overuse of prophylactic antiemetic drugs in a hospital setting. More important, no study, to our knowledge, has performed a large-scale investigation into the pattern of prescribing prophylactic antiemetics for lower emetic risk groups. The present study aimed to investigate the pattern of prescribing prophylactic antiemetic drugs using a Japanese nationwide database that contains data submitted from the designated cancer hospitals.

Key Points

Question To what extent are prophylactic antiemetic drugs prescribed for patients undergoing chemotherapy with minimal or low emetic risk?

Findings This secondary analysis of a Japanese health insurance claims database linked with a hospital-based cancer registry illustrated that among patients receiving chemotherapy with low emetic risk, 47.8% of the chemotherapy administration involved patients who were prescribed a serotonin receptor antagonist and dexamethasone. Although no prophylactic antiemetic drugs were recommended by any of the clinical practice guidelines, 12.4% of the chemotherapy with minimal emetic risk included prescription of an antiemetic drug.

Meaning This result shows a potential overuse of prophylactic antiemetic drugs to patients undergoing chemotherapy with minimal and low emetic risk.

Methods

Data Source

This study is a secondary analysis of health insurance claims data linked with the hospital-based cancer registry,[25] which were collected for research on evaluating the quality of health care for patients with cancer.[26] Most of the participating hospitals were among 397 Cancer Care Hospitals designated by the Ministry of Health, Labor, and Welfare, Tokyo, Japan. We analyzed these data for patients diagnosed in 2011 with breast, lung, colorectal, stomach, cervical, and prostate cancer. We extracted the insurance claim data from September 1, 2010, through December 31, 2012, from 122 voluntarily participating hospitals that provided data. The complete hospital-based cancer registry is estimated to contain reports on 66.9% of the new cancer cases in 2011 for all of Japan.[25] The hospitals that we sampled for this study are estimated to have provided care to 18.9% of the new patients with cancer in 2011. We analyzed data on patients with any of the 7 cancers in the database, 20 years or older, who received intravenous chemotherapy with minimal or low emetic risk. We excluded data on patients who had advanced clinical stages of cancer, specifically TNM stage IV clinical classification of malignant tumors. The institutional review board at the National Cancer Center in Japan approved this study. Owing to the retrospective nature of the database analysis, the need for informed consent was waived.

Identification of Chemotherapy Claims

We identified claims for intravenous chemotherapy with minimal or low emetic risks based on the Japanese Society of Clinical Oncology clinical practice guidelines 2010 for antiemesis

in oncology.[8] The list of chemotherapeutic agents included in this study is shown in eTable 1 in the Supplement. According to the Japanese Society of Clinical Oncology guidelines,[8] the emetic risks of some drugs depend on dosage. Dosages of methotrexate sodium of greater than 250, 50 to 250, and less than 50 mg/m^2 have moderate, low, and minimal emetic risks, respectively. Dosages of cytarabine of greater than 200, 100 to 200, and less than 100 mg/m^2 have moderate, low, and minimal emetic risks, respectively. Information about the patient's body surface area was not available in the health insurance claims or the hospital-based cancer registry. Therefore, for the purpose of our analysis, we classified methotrexate sodium dosages of greater than 250, 50 to 250, and less than 50 mg as moderate, low, and minimal emetic risk, respectively, based on the average Japanese body surface area. We also classified cytarabine dosages of greater than 200, 100 to 200, and less than 100 mg as moderate, low, and minimal emetic risk, respectively.

Statistical Analysis

Data were analyzed from March 20, 2014, to June 30, 2016. We examined the pattern of prescribing prophylactic antiemetic drugs, including neurokinin 1 (NK_1) receptor antagonists, serotonin receptor antagonists, and dexamethasone, for patients who received intravenous chemotherapy with minimal or low emetic risk. The percentage of patients receiving chemotherapy who were given prophylactic antiemetic drugs was calculated. The unit of analysis was chemotherapy administration, which was defined as the day on which the patient received chemotherapy. The patients' emetic risk was classified based on the highest risk category among the chemotherapeutic agents prescribed on the same day. A patient was counted 2 or more times if he or she received chemotherapy multiple times. The SEs were adjusted for the clustering of chemotherapy administration within patients using Huber-White estimators.[27] Antiemetic drugs that were prescribed on the same day as chemotherapeutic agents were regarded as prophylactic. We calculated the percentage of patients with chemotherapy administration who were prescribed antiemetic drugs according to cancer sites and clinical stages and conducted a 2-sided χ^2 test.

We also performed an additional analysis to confirm the robustness of the results by limiting the sample population to men 65 years or older. These patients were considered to be at low risk for CINV.[28] We performed these analyses to test whether physicians based their decision of whether to use prophylactic antiemetic drugs on the individual patient's condition. If they did, the percentage of patients who were prescribed prophylactic antiemetic drugs in this group would be less than in the younger population, by the limitation of the sample. To estimate potential savings, the cost of unnecessary antiemetic drugs, according to recommendations from the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology, was examined using the Japanese National Health Insurance drug price list from 2011 (http://www.okusuri110.com/yaka/yaka_search.html). All analyses were performed using STATA software (version 13.1; StataCorp).

Results

We extracted 73 577 occurrences of chemotherapy administration that had low (n = 50 958) or minimal (n = 22 619) emetic risk for 8545 patients (5886 women [68.9%] and 2659 men [31.1%]; mean [SD] age, 61.9 [12.8] years). There were 2464 patients in the minimal risk group and 6081 patients in the low risk group. The characteristics of the sampled patients are shown in eTable 1 in the Supplement. The mean (SD) age at the time of diagnosis was 61.1 (12.6) years in the minimal emetic risk group and 62.2 (12.9) years in the low emetic risk group. In the minimal emetic risk group, 2100 patients (85.2%) were women, and 1890 (76.7%) had breast cancer. In the low emetic risk group, 3786 patients (62.3%) were women, 2841 (46.7%) had breast cancer, and 1683 (27.7%) had lung cancer. Trastuzumab (1878 of 2464 [76.2%]) was the most frequently used chemotherapeutic agent in the minimal emetic risk group. Paclitaxel (2037 of 6081 [33.5%]), fluorouracil (848 of 6081 [13.9%]), and etoposide (597 of 6081 [9.8%]) were the most frequently prescribed chemotherapeutic agents in the low emetic risk group.

Table 1 and **Table 2** show the percentages of chemotherapy administration where the patient was prescribed prophylactic antiemetic drugs for chemotherapy with minimal or low emetic risk. Although no prophylactic antiemetic drugs were recommended by any of the clinical practice guidelines, 12.4% of the chemotherapy with minimal emetic risk was accompanied by an antiemetic drug. Specifically, 6.3% (95% CI, 5.4%-7.4%) of the chemotherapy with minimal emetic risk involved prescription of dexamethasone; 2.9% (95% CI, 2.2%-3.7%), prescription of a serotonin receptor antagonist; and 2.8% (95% CI, 2.2%-3.4%), prescription of a serotonin receptor antagonist and dexamethasone. Among patients in the low emetic risk group, 47.8% (95% CI, 46.5%-49.2%) of the chemotherapy included prescription of a serotonin receptor antagonist and dexamethasone. Occasionally (2.8%; 95% CI, 2.5%-3.1%), chemotherapy with minimal emetic risk included prescription of a combination of an NK_1 receptor antagonist, a serotonin receptor antagonist, and dexamethasone.

In the minimal emetic risk group, 87.9% of the chemotherapy was administered at an outpatient clinic. In the outpatient group, 5.2% (95% CI, 4.2%-6.3%) of the chemotherapy with minimal emetic risk included prescription of dexamethasone, whereas 10.8% (95% CI, 8.8%-13.2%) of the chemotherapy with minimal emetic risk administered to inpatients in this group included prescription of an serotonin receptor antagonist and dexamethasone, and 16.8% (95% CI, 12.8%-21.6%) included prescription of a serotonin receptor antagonist.

In the low emetic risk group, 27.3% of the chemotherapy was administered to inpatients. In the inpatient group, 33.7% (95% CI, 31.7%-35.9%) of the chemotherapy included the prescription of a serotonin receptor antagonist and dexamethasone. In the outpatient group, 53.1% (95% CI, 51.6%-54.7%) of the chemotherapy included the prescription of a serotonin receptor antagonist and dexamethasone.

In both emetic risk groups, the frequency of chemotherapy that involved the prescription of potentially unnecessary antiemetic drugs differed significantly among clinical

Table 1. Percentages of Prophylactic Antiemetics Prescribed for Chemotherapy With Minimal Emetic Risk

Guideline Recommendations		Antiemetic Prescribed	Chemotherapy Administration, % (95% CI)
ASCO/JSCO	MASCC		
All chemotherapy[a]			
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist + dexamethasone	0.1 (0.1-0.2)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	2.8 (2.2-3.4)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	0.2 (0.1-0.3)
Overuse	Overuse	NK_1 receptor antagonist	0.1 (0.1-0.2)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	0.1 (0.1-0.20)
Overuse	Overuse	Serotonin receptor antagonist	2.9 (2.2-3.7)
Overuse	Overuse	Dexamethasone	6.3 (5.4-7.4)
Appropriate	Appropriate	None[b]	87.6 (86.2-88.9)
Inpatient chemotherapy[c]			
Overuse	Overuse	NK1 receptor antagonist + serotonin receptor antagonist + dexamethasone	0.2 (0.1-0.5)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	10.8 (8.8-13.2)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	1.1 (0.6-1.9)
Overuse	Overuse	NK_1 receptor antagonist	0.3 (0.1-0.6)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	0.2 (0.1-0.4)
Overuse	Overuse	Serotonin receptor antagonist	16.8 (12.8-21.6)
Overuse	Overuse	Dexamethasone	14.8 (12.5-17.4)
Appropriate	Appropriate	None[d]	55.9 (51.6-60.1)
Outpatient chemotherapy[e]			
Overuse	Overuse	NK1 receptor antagonist + serotonin receptor antagonist + dexamethasone	0.1 (0.1-0.2)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	1.6 (1.2-2.2)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	0.0 (0.0-0.2)
Overuse	Overuse	NK_1 receptor antagonist	0.1 (0.0-0.1)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	0.1 (0.1-0.2)
Overuse	Overuse	Serotonin receptor antagonist	0.9 (0.6-1.4)
Overuse	Overuse	Dexamethasone	5.2 (4.2-6.3)
Appropriate	Appropriate	None[f]	92.0 (90.7-93.1)

Abbreviations: ASCO, American Society of Clinical Oncology; JSCO, Japanese Society of Clinical Oncology; MASCC/ESMO, Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology; NK_1, neurokinin 1.

[a] Includes 22 619 chemotherapy administrations.

[b] Includes prescription of dopamine receptor antagonists in 0.7% (95% CI, 0.5-0.9).

[c] Includes 2734 chemotherapy administrations.

[d] Includes prescription of dopamine receptor antagonists in 1.8% (95% CI, 1.2-2.5).

[e] Includes 19 885 chemotherapy administrations.

[f] Includes prescription of dopamine receptor antagonists in 0.3% (95% CI, 0.2%-0.4%).

stages and cancer sites (**Table 3**). Frequencies for clinical stage ranged from 3.0% (95% CI, 1.2%-7.4%) for stage 0 cancer to 26.1% (95% CI, 22.7%-29.7%) for stage III cancer in the minimal emetic risk group and from 36.5% (95% CI, 27.0%-47.1%) for stage 0 cancer to 52.9% (95% CI, 50.7%-55.2%) for stage III cancer in the low emetic risk group ($P < .001$). Frequencies ranged from 2.3% (95% CI, 1.7%-3.2%) for breast cancer to 53.0% (95% CI, 47.9%-58.0%) for lung cancer in the minimal emetic risk group and from 27.3% (95% CI, 20.3%-35.7%) for prostate cancer to 60.6% (95% CI, 58.8%-62.3%) for breast cancer in the low emetic risk group ($P < .001$).

We identified 15 074 occurrences of chemotherapy administration for men who were 65 years or older among the patients in this study. Of these, 13.9% (95% CI, 10.1%-18.9%) in the minimal emetic risk group included prescription of the 2-drug combination of a serotonin receptor antagonist and dexamethasone, and 8.9% (95% CI, 6.2%-12.6%) included prescription of a serotonin receptor antagonist. In the low emetic risk group, 38.9% (95% CI 36.0%-42.0%) included prescription of the 2-drug combination of a serotonin receptor antagonist and dexamethasone. Moreover, hospitalization for chemotherapy occurred in 38% of administrations in the minimal emetic risk group and 48.6% in the low emetic risk group. Inpatients in minimal emetic risk groups were less frequently prescribed a serotonin receptor antagonist and dexamethasone (17.6%; 95% CI, 12.9%-23.6%) compared with inpatients in low emetic risk groups (32.6%; 95% CI, 29.1%-36.3%). The detailed results of this analysis are described in eTables 2 and 3 in the Supplement.

The cost of the prophylactic antiemetic drugs was approximately ¥170 million (US $1.6 million). This cost included ¥7 million (US $70 000) and ¥ 160 million (US $1.5 million) for the chemotherapy administration with minimal and low emetic risk, respectively.

Table 2. Percentages of Prophylactic Antiemetics Prescribed for Chemotherapy With Low Emetic Risk

Guideline Recommendation		Antiemetic Prescribed	Chemotherapy Administration, % (95% CI)
ASCO/JSCO	MASSC/EMSO		
All chemotherapy[a]			
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist + dexamethasone	2.8 (2.5-3.1)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	47.8 (46.5-49.2)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	0.2 (0.2-0.3)
Overuse	Overuse	NK_1 receptor antagonist	0.3 (0.2-0.4)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	1.6 (1.4-1.9)
Overuse	Appropriate	Serotonin receptor antagonist	4.5 (3.9-5.1)
Appropriate	Appropriate	Dexamethasone	36.2 (34.9-37.5)
Underuse	Underuse	None[b]	6.7 (5.7-7.7)
Inpatient chemotherapy[c]			
Overuse	Overuse	NK1 receptor antagonist + serotonin receptor antagonist + dexamethasone	4.2 (3.6-4.9)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	33.7 (31.7-35.9)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	0.6 (0.4-1.0)
Overuse	Overuse	NK_1 receptor antagonist	0.9 (0.6-1.4)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	5.1 (4.3-6.1)
Overuse	Appropriate	Serotonin receptor antagonist	6.3 (5.3-7.5)
Appropriate	Appropriate	Dexamethasone	33.6 (31.5-35.7)
Underuse	Underuse	None[d]	15.6 (12.7-18.9)
Outpatient chemotherapy[e]			
Overuse	Overuse	NK1 receptor antagonist + serotonin receptor antagonist + dexamethasone	2.2 (1.9-2.6)
Overuse	Overuse	Serotonin receptor antagonist + dexamethasone	53.1 (51.6-54.7)
Overuse	Overuse	NK_1 receptor antagonist + serotonin receptor antagonist	0.1 (0.0-0.2)
Overuse	Overuse	NK_1 receptor antagonist	0.1 (0.0-0.1)
Overuse	Overuse	NK_1 receptor antagonist + dexamethasone	0.3 (0.2-0.5)
Overuse	Appropriate	Serotonin receptor antagonist	3.8 (3.1-4.6)
Appropriate		Dexamethasone	37.1 (35.6-38.7)
Underuse	Underuse	None[f]	3.3 (2.8-3.9)

Abbreviations: ASCO, American Society of Clinical Oncology; JSCO, Japanese Society of Clinical Oncology; MASCC, MASCC/ESMO, Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology; NK_1, neurokinin 1.

[a] Includes 50 958 chemotherapy administrations.

[b] Includes prescription of dopamine receptor antagonists (which were considered appropriate in MASCC/ESMO guidelines but not recommended in the JSCO or ASCO guidelines) in 0.7% (95% CI, 0.5%-0.9%).

[c] Includes 13 911 chemotherapy administrations.

[d] Includes prescription of dopamine receptor antagonists (which were considered appropriate in MASCC/ESMO guidelines but not recommended in the JSCO or ASCO guidelines) in 1.8% (95% CI, 1.2%-2.5%),

[e] Includes 37 047 chemotherapy administrations.

[f] Includes prescription of dopamine receptor antagonists (which were considered appropriate in MASCC/ESMO guidelines but not recommended in the JSCO or ASCO guidelines) in 0.3% (95% CI, 0.2%-0.4%).

Discussion

We found that a substantial number of patients in Japan receiving chemotherapy with minimal or low emetic risk were prescribed prophylactic antiemetic drugs, even when antiemetic guidelines do not recommend their use. More than 10% of the chemotherapy with minimal emetic risk involved the prescription of at least 1 antiemetic, and about half of the chemotherapy in the low emetic risk group included a combination of 2 antiemetic drugs. Given that chemotherapy with minimal and low emetic risk is reported to cause emesis approximately 10% and 30% of the time, respectively, a 10% prescription rate for the minimal emetic risk group may be reasonable if these patients are accurately identified, but the antiemetic use for the low emetic risk group in this study was far higher than expected. Furthermore, outpatients were more frequently prescribed a 2-drug combination of antiemetics in the low emetic risk group than were inpatients. Because we expect outpatients to be in a much better condition than inpatients, those patients are likely being prescribed antiemetic drugs regardless of their condition. In the minimal emetic risk group, patients with a more advanced stage of cancer tended to be prescribed antiemetic drugs more often, whereas patients in the low emetic risk group had similar rates of antiemetic drug prescription among those with clinical stages I to III cancer. Patients with colorectal or lung cancer in the minimal emetic risk group received antiemetic drugs more often than patients with other cancers. This finding can be explained by the fact that patients with colorectal or lung cancer in the minimal emetic risk group (stage III, 49.0% of chemotherapy

administration for patients with colorectal cancer and 63.7% of chemotherapy administration for patients with lung cancer) treated more advanced stage cancer compared with other types of cancer in this group (16.6%-28.2%). Cancer prognosis itself leads to nausea and vomiting, so clinicians may prescribe antiemetic drugs more often for those patients. Our study revealed an opportunity to improve clinical practice by reducing unnecessary care and allocating resources to effective treatment, in particular for the low emetic risk group.

One possible reason for the overuse of prophylactic antiemetic drugs is that physicians and patients are too concerned about the adverse effects of chemotherapy that could result in the cessation of the patients' chemotherapy. This possibility is supported by a report that found that poorly controlled CINV led to a delay or refusal of possibly life-saving chemotherapy in 25% to 50% of patients.[29,30] Nevertheless, the frequency of CINV in patients receiving chemotherapy with low or minimal emetic risk is less than 30%, meaning that most of the prophylactic treatment, if provided, may not be necessary. Furthermore, antiemetic drugs carry a risk for adverse effects, including mild headache, transient elevation of hepatic aminotransferase levels, and constipation,[31,32] which can also interfere with chemotherapy. Furthermore, prescribing unnecessary medication imposes a financial burden on patients. Physicians and other health care professionals should discuss the benefit and harm of these antiemetic drugs with patients before prescribing the drugs.

Another factor that may contribute to overuse of antiemetic drugs is the packaging of these drugs with chemotherapy regimens. Despite more chemotherapeutic agents with low and minimal emetic risk becoming available,[20] to our knowledge, the necessity of antiemetic prophylaxis has never been tested. Because these agents induce little emesis to begin with, but given the lack of clinical evidence, anxiety about CINV experienced in previous chemotherapy regimens with moderate emetic risk may have been applied to the newer drugs despite their having lower emetogenicity. This anxiety could lead to the inclusion of prophylactic antiemetic drugs in future chemotherapeutic regimens and potentially contribute to the overuse of antiemetic drugs.[20] We also found similar levels of use in a demographic of patients who are generally better at controlling their vomiting[33] relative to the overall patient population, which indicates that the use of antiemetic drugs for chemotherapy with low and minimal emetic risk is predetermined, regardless of the individual patient's risk. Recent studies have suggested the importance of identifying a patient's individual risk for CINV.[34,35] Hospitals should reevaluate their registered chemotherapy regimen to enhance appropriate use of antiemetic drugs.

Inpatients in the minimal emetic risk group were frequently prescribed prophylactic antiemetic drugs. In our study, men 65 years or older were more often hospitalized for their chemotherapy and prescribed antiemetic drugs than the rest of the study patients. Elderly patients are at a higher risk for complications related to CINV, such as dehydration, hypotension, and renal impairment.[36] If elderly patients experience CINV during their chemotherapy, such adverse effects could worsen. This finding may explain why more elderly patients were hospitalized and then prescribed prophylactic antiemetic drugs compared with other patients.

Table 3. Prescription of Prophylactic Antimetics for Chemotherapy With Minimal and Low Emetic Risk by Clinical Stage and Cancer Site

	Chemotherapy Administration, % (95% CI)	
	Minimal Risk Group (n = 22 619)[a]	Low Risk Group (n = 50 958)[b]
Clinical stage		
0	3.0 (1.2-7.4)	36.5 (27.0-47.1)
I	9.2 (7.3-11.7)	52.1 (49.1-55.2)
II	6.6 (5.2-8.3)	54.8 (52.6-56.9)
III	26.1 (22.7-29.7)	52.9 (50.7-55.2)
Cancer site		
Stomach	30.6 (20.1-43.6)	47.3 (41.4-53.2)
Colorectal	46.0 (37.7-54.5)	35.4 (31.1-39.8)
Breast	2.3 (1.7-3.2)	60.6 (58.8-62.3)
Lung	53.0 (47.9-58.0)	50.9 (48.5-53.3)
Prostate	28.2 (13.9-49.1)	27.3 (20.3-35.7)
Cervix	21.0 (7.7-45.8)	44.3 (34.6-54.6)

[a] Includes prescription of neurokinin 1 (NK_1) receptor antagonist, serotonin receptor antagonist, and/or dexamethasone.

[b] Includes prescription of a 3-drug combination (NK_1 receptor antagonist, serotonin receptor antagonist, and dexamethasone), a 2-drug combination (serotonin receptor antagonist and/or dexamethasone and/or NK_1 receptor antagonist), or an NK_1 receptor antagonist.

Limitations

Our study has several limitations. First, prophylactic antiemetic drugs were defined as those prescribed on the same day as chemotherapy. The antiemetic drugs may actually not be prophylactic but rather therapeutic, resulting in the overestimation of the overuse. Second, oral antiemetic drugs prescribed before the first day of chemotherapy were not taken into account. This process might have caused underestimation of the actual rates of use. Third, physicians' clinical judgment and patients' preferences were not taken into consideration. Such data, including previous experiences of CINV and patients' comorbidities, were not available from the health insurance claims database or the hospital-based cancer registry. Hesketh et al[37] suggested that among patients with cancer who had a history of CINV and received chemotherapy with a low emetic risk, palonosetron hydrochloride was effective in preventing CINV in the acute and delayed postchemotherapy phases. Reasons for and consequences of the use of prophylactic antiemetic drugs should be examined in future studies. Finally, the exact drug dosages and the body surface area of patients were not available from the claims data. Consequently, the emetic risks of patients undergoing chemotherapy using methotrexate and cytarabine may be misclassified. However, in our sample, few patients used these drugs for chemotherapy, and the influence of this misclassification does not seem to be a major concern.

Conclusions

This study illustrates the potential for overuse of prophylactic antiemetics for chemotherapy with minimal and low emetic risks. Prescribing unnecessary antiemetic drugs not only

exposes patients to the risk for adverse effects but also produces an economic burden on society. Future examination of the reasons for and consequences of antiemetic overuse will be important to improve the quality of care.

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