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Inclusion of medications considered potentially inappropriate in older adults in chemotherapy templates for hematologic malignancies: one recommendation for all?

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Abstract

Background: There remains a paucity of data regarding the use of potentially inappropriate medications (PIMs) in the supportive management of older adults undergoing chemotherapy. Raising awareness among healthcare providers of the frequency of their use and potential toxicities may help to minimize the risks to patients.

Objective: To evaluate the frequency of six specific classes of medications considered PIMs by the American Geriatrics Society Beers Criteria that are commonly included in the National Comprehensive Cancer Network (NCCN) chemotherapy order templates for hematologic malignancies. The six PIMs evaluated are first generation antihistamines, benzodiazepines, corticosteroids, H_2-receptor antagonists, metoclopramide, and antipsychotics.

Methods: A total of 311 unique chemotherapy order templates published online by the NCCN for treatment of hematologic malignancies were reviewed to determine the frequency that these six specific PIMs were recommended for supportive care.

Results: Approximately 45 percent of the NCCN chemotherapy templates for hematologic malignancies specifically recommended the use of at least one of the six PIMs examined. The remainder of the templates evaluated referred exclusively to the (NCCN Guidelines®) Oncology for Antiemesis, which also included the use of at least one of the six PIMs evaluated.

Conclusions: These findings demonstrate that PIMs are frequently used as supportive therapy in the treatment of hematologic malignancies. Increasing healthcare provider awareness of their potential side effects may minimize the risks associated with their use in older adults with hematologic malignancies undergoing chemotherapy.

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1. Introduction

Increasing age is directly related to an increasing risk of cancer, and older adults comprise the majority of cancer diagnoses in the United States [1]. It is estimated that by 2030, nearly 20% of adults in the United States will be ≥ 65 years of age, and that the absolute number will double by 2050 [2]. Hematologic malignancies are frequently diagnosed in older adults, and the median age at diagnosis for diseases such as myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and multiple myeloma is ≥ 65 years of age [1].

Recently, the need to improve the evidence base for treating older adults with cancer was highlighted by both the Institute of Medicine (IOM) and the American Society of Clinical Oncology (ASCO) [3, 4]. Despite the initiative to increase the inclusion of older adults in clinical trials, there remains a paucity of data regarding the use of potentially inappropriate medications (PIMs) in the supportive management of older adults undergoing chemotherapy. Geriatric impairments are highly prevalent in older adults with hematologic malignancies [5], and intensive induction therapy can lead to decreases in physical function that may increase the risk for complications such as falls [6, 7]. The use of antihistamines, corticosteroids, and benzodiazepines for the management of chemotherapy-related side effects, although oftentimes necessary, may lead to additional toxicities that could further exacerbate the risk for adverse outcomes. For example, first generation antihistamines are associated with sedation, cognitive impairment, and falls [8], which could further increase the risk for complications in older adults with decreased physical function as a result of their chemotherapy treatment.

The American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults is a widely consulted resource regarding the safety of specific medications for older adults [9]. The AGS Beers Criteria include an explicit list of PIMs that are best avoided or used with caution in older adults, as the potential risks of these medications may outweigh the benefits, and safer alternatives may exist [9]. The National Comprehensive Cancer Network (NCCN) provides evidence-based guidelines for the treatment and management of patients with cancer [10], and publishes a collection of chemotherapy templates of standard treatment regimens [11]. In this study, we evaluated the frequency of six specific medications considered PIMs by the AGS Beers Criteria that are included in the NCCN chemotherapy order templates for hematologic malignancies. Our aim was to document the frequency with which these agents are included in standard treatment regimens for hematologic malignancies. The goal of this study was not to advocate for the elimination of PIMs as supportive therapies in older adults undergoing chemotherapy, but rather to draw attention to the potential risks associated with these PIMs, and to suggest strategies to minimize their toxicity.

2. Methods

This study included no human subjects and was exempt from human subjects committee review. There were a total of 311 unique chemotherapy order templates for hematologic malignancies published online by the NCCN [11] as of February 20, 2017. Two authors (A.Z. and T.W.) reviewed all 311 chemotherapy order templates as well as the NCCN

Guidelines® for Antiemesis Version 2.2015 which was the most current version at the time of review [12], and extracted information regarding whether each template made specific recommendations regarding the use of first generation antihistamines, benzodiazepines, corticosteroids, H_2-receptor antagonists, metoclopramide, or antipsychotics as supportive therapy. Corticosteroids included in the template as part of the treatment regimen and not as supportive therapy were not included in the analysis.

These six medications were chosen because they are commonly used as premedications or antiemetics in treatment regimens for hematologic cancers. All six medications are identified as PIMs under Table 2 ("Medications to avoid for many or most older adults") and Table 3 ("Medications for older adults with specific diseases or syndromes to avoid") of the 2015 American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults list [9]. These six medications are also listed as medications commonly used for supportive care that are of concern in older patients in the NCCN Guidelines® for Older Adult Oncology Version 2.2015 [13]. The frequency of the six PIMs evaluated was tabulated by disease type. IBM SPSS Statistics for Windows, Version 23, statistical software (IBM Corp., Armonk, N.Y., USA) was utilized for descriptive statistics, including frequencies.

3. Results

A total of 311 unique chemotherapy order templates were reviewed, detailing treatment regimens for 16 types of hematologic cancers (Electronic Supplemental Material Table S1). Approximately 45 percent (142 templates) of the chemotherapy order templates recommended the use of at least one of the 6 PIMs examined within the template. The remainder of the NCCN chemotherapy templates examined referred to the NCCN Guidelines for Antiemesis [12] for recommendations regarding antiemetic prophylaxis and management.

3.1 First generation antihistamines

Diphenhydramine was the most common first generation antihistamine found in the NCCN chemotherapy order templates examined. One hundred and twenty three chemotherapy templates (39.5%) examined recommended the use of diphenhydramine as supportive therapy. The maximum single dose of diphenhydramine ranged from 50 to 100 mg and the majority of the templates gave no specific preference for intravenous (IV) versus oral (PO) route of administration. Use of diphenhydramine was most common in chemotherapy templates for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, lymphoplasmacytic lymphoma, and diffuse large B-cell lymphoma (DLBCL). Diphenhydramine was also listed in the NCCN Guidelines for Antiemesis [12] as an option for management of dystonic reactions to metoclopramide at a dose of 25 – 50 mg PO or IV every 4 to 6 hours.

3.2 Benzodiazepines

The most commonly recommended benzodiazepine was lorazepam at a dose and frequency of 0.5 – 2 mg PO, IV, or sublingual every 4 to 6 hours as needed. Only 18 NCCN

chemotherapy order templates (5.8%) made specific recommendations regarding the use of benzodiazepines as supportive therapy. The maximum 24 hour dose of lorazepam was 12 mg for all 18 templates. Acute promyelocytic leukemia (APL) and primary central nervous system (CNS) lymphoma were the most frequent cancers with templates that recommended the use of a benzodiazepine. Lorazepam was also recommended as an option for breakthrough treatment of chemotherapy-induced nausea/vomiting by the NCCN Guidelines for Antiemesis [12], at a dose of 0.5 – 2 mg PO/SL/IV every 6 hours as needed.

3.3 Corticosteroids

Dexamethasone was the most commonly used corticosteroid, with maximum 24 hour doses ranging from 4 mg to 36 mg. Thirty one NCCN chemotherapy order templates (9.9%) specifically recommended the use of dexamethasone as premedication or for anti-emesis management. A majority of the chemotherapy order templates for APL and primary CNS lymphoma made recommendations for the use of dexamethasone as supportive therapy. In APL, 8 out of 23 chemotherapy order templates recommended the use of dexamethasone, with 24 hour doses ranging from 12 to 20 mg. One template specifically recommended a lower total 24 hour dose of 8 mg for patients who were over 70 years of age. In primary CNS lymphoma, 9 out of 16 chemotherapy order templates recommended the use of dexamethasone, with 24 hour doses ranging from 12 to 16 mg.

Corticosteroids were also included in the NCCN Guidelines for Antiemesis [12]. For IV chemotherapeutic agents with low emetic risk, dexamethasone 12 mg PO/IV daily is recommended for emesis prevention and can be repeated for multiday doses of chemotherapy. For IV chemotherapeutic agents classified as high or moderate emetic risk, dexamethasone 12 mg or 20 mg daily PO/IV prior to and/or at 8 mg PO/IV for several days following administration of chemotherapy is recommended, in combination with neurokinin (NK1) receptor antagonists or serotonin-5-$(HT)_3$-receptor antagonists. Dexamethasone was also recommended for breakthrough chemotherapy-induced nausea/vomiting at a dose of 12 mg PO/IV daily.

3.4 H_2-Receptor Antagonists

Twenty of the NCCN chemotherapy order templates examined (6.4%) made specific recommendations regarding the use of H_2-receptor antagonists as supportive therapy. The highest frequencies were found in APL and primary CNS lymphoma. Additionally, 70 NCCN chemotherapy order templates (22.5%) recommended consideration of an H_2-receptor antagonist or a proton pump inhibitor as supportive therapy.

3.5 Metoclopramide

Five NCCN chemotherapy order templates (1.6%) made specific recommendations for the use of metoclopramide as supportive therapy. The use of metoclopramide was most frequently found in APL, with 4 templates recommending the use of metoclopramide for anti-emesis management. Metoclopramide was also recommended as an option for emesis prevention in low and minimal emetic risk IV chemotherapy, as breakthrough treatment for chemotherapy-induced nausea/vomiting, and as emesis prevention in oral chemotherapeutic

agents by the NCCN Guidelines for Antiemesis [12]. The recommended dose was 10 – 40 mg PO/IV daily every 4 or every 6 hours as needed.

3.6 Antipsychotics

There were no individual NCCN chemotherapy order templates that made specific recommendations regarding the use of antipsychotics as supportive therapy, however, olanzapine is recommended as an option in the NCCN Guidelines for Antiemesis [12] for the prevention of acute and delayed emesis for high or moderate emetic risk chemotherapeutic agents in combination with dexamethasone. The NCCN Guidelines for Antiemesis also list olanzapine as an option for breakthrough treatment of chemotherapy-induced nausea and vomiting at a dose of 10 mg PO daily for 3 days.

4. Discussion

The NCCN publishes a collection of up to date, evidence-based chemotherapy order templates to guide the treatment and management of a variety of solid and hematologic malignancies, and is a commonly utilized resource for practicing oncologists [11]. Our study shows that PIMs are frequently recommended as supportive therapy in the treatment of hematologic malignancies. Almost half (45%) of the NCCN chemotherapy order templates for hematologic malignancies made specific recommendations for the use of PIMs as supportive therapy, and the remainder of the templates refer to the NCCN Guidelines for Antiemesis [12], which also includes the use of PIMs in anti-emesis management. First generation antihistamines and corticosteroids comprised the majority of PIMs that were specifically recommended within the templates, whereas recommendations for metoclopramide, benzodiazepines, and antipsychotics were relatively infrequent.

The goal of this study was not to advocate for elimination of PIMs as supportive therapies in older adults undergoing chemotherapy for hematologic malignancies, nor was it to criticize the recommendations made by the NCCN. Rather, the purpose was to draw attention to the frequency with which PIMs are included as supportive care in chemotherapy regimens used to treat hematologic malignancies, to highlight the potential risks associated with their use, and to suggest strategies to minimize their toxicity. Strategies may include using the lowest effective dose, selecting alternative agents when the risk/benefit ratio for use of a supportive care PIM is too high, and educating patients and caregivers on their potential toxicities. For example, if alternative agents such as NK1 receptor antagonists or serotonin-5-$(HT)_3$-receptor antagonists can be used, then these agents should be preferentially considered over agents such as metoclopramide, benzodiazepines, or antipsychotics for emesis prevention [14], as these agents have not been associated with adverse outcomes in older adults [15, 16]. In situations where the use of corticosteroids or diphenhydramine may be necessary, patients and caregivers should be educated regarding the potential side effects and the need for closer monitoring to prevent adverse outcomes such as falls.

PIMs listed by the AGS Beers Criteria are divided into several categories, such as “medications to avoid for many or most older adults”, “medications to avoid for older adults with specific diseases or syndromes”, and “medications to be used with caution”. Table 1 provides a summary of the effects of the 6 PIMs evaluated in this study along with

recommendations for management to minimize toxicities. First generation antihistamines such as diphenhydramine are listed under the AGS Beers category of medications to avoid for many or most older adults. Diphenhydramine is associated with sedation and cognitive impairment and should be avoided, especially in older adults with delirium [9]. Diphenhydramine clearance is significantly slowerin older adults, which can cause confusion, dry mouth, and constipation [17–19]. These side effects can worsen delirium and increase the risk of falls and injury [20]. Higher cumulative anticholinergic use has also been associated with an increased risk for dementia [21]. In the chemotherapy order templates that were reviewed, single doses as high as 100 mg of diphenhydramine were included, which raises concern, as significant psychomotor impairment has been observed in healthy elderly volunteers with dosages higher than 50 mg [22]. Metoclopramide is also listed under the AGS Beers category of medications to avoid for many or most older adults and can cause extrapyramidal effects, including tardive dyskinesia, especially in frail older adults [23, 24].

Benzodiazepines and antipsychotics are listed under the AGS Beers category of medications to avoid for many or most older adults and older adults with delirium or falls. In general, all benzodiazepines can increase the risk of cognitive impairment, delirium, falls, and fractures in older adults, and more recent initiation is associated with a greater risk of falls [25]'[26]. Older adults also have increased sensitivity to benzodiazepines and decreased metabolism of long acting agents [26]. In the NCCN chemotherapy order templates reviewed, the total recommended dosages of lorazepam in a 24 hour period could be as high as 12 mg, which is concerning as higher total doses of benzodiazepines are associated with a greater risk of falls with injuries [27, 28]. Antipsychotics such as olanzapine can increase the risk of cerebrovascular accident (CVA) [29], and are associated with a greater rate of cognitive decline and mortality in older adults with dementia [30]. Antipsychotics should also be avoided in older adults with a history of falls or fractures, as these agents can cause ataxia, impair psychomotor function, and induce syncope leading to additional falls [31, 32].

Corticosteroids and H_2-receptor antagonists are listed under the category of medications to avoid in older adults with specific diseases or syndromes, such as delirium or falls. Corticosteroids are associated with cognitive impairment and worsening delirium in older adults [33]. The dosage of corticosteroids can also impact the incidence of CNS toxicity, with those receiving > 80 mg of prednisone or the equivalent being at the highest risk for developing acute psychiatric reactions [34, 35]. H_2-receptor antagonists are associated with CNS toxicities such as confusion, disorientation, agitation, and hostility and should be avoided in older adults with delirium [36]. Furthermore, it has been noted that standard doses of H_2 receptor antagonists may lead to a higher risk of adverse drug events and mortality in older adults, as age-related decreases in glomerular filtration rate may decrease excretion of H_2-receptor antagonists [33, 37].

Assessing individual risk of severe toxicity from chemotherapy is important for all patients undergoing chemotherapy, but is especially important for older adults who may have significant variability in their health status and functional reserve. Tools to predict the risk of chemotherapy toxicity in older adults have been developed [38, 39], but have not been validated to specifically predict emesis risk and the associated complications in older adults undergoing chemotherapy. Interestingly, there have been data to suggest that older patients

are less likely to experience chemotherapy-induced nausea and vomiting compared to younger patients [40–42], which may be relevant when selecting antiemetic agents. Development of tools to identify individuals who is at increased risk for treatment-related emesis are needed to better assess the risks and benefits of utilizing PIMs as supportive therapies in older adults undergoing chemotherapy.

There are several limitations to our study. Specifically, we did not evaluate the frequency of all potential PIMs identified by the AGS Beers criteria that are recommended in the NCCN chemotherapy order templates. The NCCN Guidelines for Older Adult Oncology list of medications commonly used for supportive care that are of concern in older patients [13] provides a more comprehensive list of PIMs that may be encountered in the treatment of older adults with cancer. Additionally, we did not focus on the precise indications for each supportive care medication in the guidelines, which are important considerations when deciding on the risks and benefits of using these medications. Also, we limited our review to the NCCN chemotherapy order templates pertaining to treatment for hematologic malignancies, and therefore did not include all published NCCN chemotherapy order templates. Another limitation of our study is that there have been updates to the NCCN chemotherapy templates and guidelines since our last review. While newer templates and guidelines have been introduced, the practice patterns reflected in our study still persist and providers should remain vigilant regarding the use of PIMs in supportive care during chemotherapy treatment. Finally, while the medications evaluated are considered PIMs, no prospective studies have evaluated the safety or risk of specific adverse outcomes of these medications when used for supportive care in older adults with cancer.

Based on the findings from this study, we recommend that clinicians consider the risk of PIMs as chemotherapy supportive care in their older patients with hematologic malignancies and consider incorporation of tools such as the AGS Beers Criteria into their therapeutic decisionmaking. This will help increase awareness and better guide clinicians treating older adults with hematologic cancers on how to minimize toxicities related to supportive therapies.

5. Conclusion

PIMs are frequently used as supportive therapy in the treatment of hematologic malignancies. Increasing awareness among healthcare providers of their potential side effects and devising methods to minimize the risks associated with their use is important in improving the management of older adults with hematologic cancers undergoing chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

Tanya Wildes receives research funding from Janssen and has consulted for Carevive Systems. Arti Hurria is a principal investigator for Celgene and Novartis and a consultant for Boehringer Ingelheim Pharmaceuticals and Pieran Biosciences. Amy Zhou, Holly Holmes, Arti Hurria and Tanya Wildes declare that they have no conflicts of interest directly relevant to the content of this study.

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Key Points:

1. Potentially inappropriate medications are frequently used as supportive therapy for older adults with hematologic malignancies undergoing chemotherapy
2. Raising awareness among healthcare providers of the frequency of their use and potential toxicities will help to implement strategies to minimize the risks to patients

Table 1:

Summary of effects and recommendations for management of specific PIMs (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Older Adult Oncology V2.2015. ©2017 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org [13])

Therapeutic class/medication	Negative effects	Condition the drug may adversely affect	Recommendation
First-generation antihistamines: diphenhydramine	Highly anticholinergic; increased risk of confusion, dry mouth, constipation, and other anticholinergic toxicities. Clearance reduced with advanced age.	Delirium Cognitive impairment Urinary retention	Use only for supportive care when convincing benefit exists, and use the lowest dose possible Appropriate for acute treatment of severe allergic reactions For pruritus, use second generation antihistamines
Benzodiazepines: lorazepam	Older adults have increased sensitivity to benzodiazepines and slower metabolism of benzodiazepines Can increase the risk of falls, cognitive impairment, and motor vehicle accidents	Falls Fractures Cognitive impairment Delirium	Reduce dose and/or lengthen the dosing interval when using for supportive care during chemotherapy administration For nausea, consider alternative antiemetics (for example, serotonin antagonists or aprepitant)
Corticosteroids (oral): dexamethasone	Can result in weight gain, muscle weakness, agitation, hyperglycemia, Cushing syndrome. Increases risk of gastrointestinal bleeding, fractures, infections, and thromboembolism.	Delirium Diabetes Osteoporosis Insomnia	When used for supportive care, carefully consider the dose and duration of therapy. Use the lowest possible dose ideally for shortterm therapy (1–3 weeks) For nausea, consider alternative antiemetics (for example, serotonin antagonists or aprepitant)
Histamine-2 receptor blockers: Famotidine ranitidine cimetidine	Can induce or worsen delirium in older adults	Delirium Cognitive impairment Dementia	Avoid in patients at risk for delirium
Antiemetic, prokinetic: metoclopramide	May cause extrapyramidal effects; risk greater in frail older adults	Parkinson's disease	Avoid, unless use for patients with gastroparesis If benefit outweighs risk, use the lowest dose possible, and avoid exceeding 5 mg For nausea, consider alternative antiemetics (for example, serotonin antagonists or aprepitant)
Antipsychotics: olanzapine	Olanzapine has high anticholinergic effects. Increases the risk of cerebrovascular accident. Increased mortality risk in patients with dementia. Can cause hyperglycemia. Increases the risk of falls and fractures, especially in patients with baseline high risk. Concern for QT prolongation, especially in combination with serotonin antagonists, antidepressants, and in patients with underlying cardiac diseases.	Dementia (black box FDA warning for increased mortality risk) Falls Fractures	May be appropriate for short duration treatment of refractory chemotherapy-induced nausea and vomiting If using an antipsychotic, attempt to reduce, taper, or stop other antipsychotics and/or drugs acting on the central nervous system that can worsen the risk of falls or cognitive decline With concern for QT prolongation, start at the lowest dose with slow uptitration. Consider baseline ECG before initiation of therapy. For nausea, could consider other antiemetics (serotonin antagonists or aprepitant for example) if risk

Therapeutic class/medication	Negative effects	Condition the drug may adversely affect	Recommendation
			outweighs the benefit of using an antipsychotic. Monitor for extrapyramidal symptoms; tools such as the AIMS are useful.

Abbreviations: PIMs = potentially inappropriate medications, NCCN = National Comprehensive Cancer Network, FDA = Food and Drug Administration, ECG = Electrocardiography, AIMS = Abnormal Involuntary Movements Scale

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