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ORIGINAL ARTICLE

Association of inappropriate polypharmacy with emergency department visits in older patients receiving anti-neoplastic therapy: a population-based study

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Abstract

Purpose We aimed to investigate the prevalence and predicting factors of inappropriate polypharmacy including potentially inappropriate medications (PIMs) and drug-drug interactions (DDIs) and their associations with emergency department (ED) visits in older Korean patients receiving anti-neoplastic therapy.

Methods We identified older patients receiving anti-neoplastic therapy in 2016 from the National Health Claims database. We investigated the prevalence of inappropriate polypharmacy comprising PIMs and DDIs in geriatric patients according to the 2019 American Geriatrics Society Beers Criteria® and chemotherapeutic DDIs using Lexicomp Online™ and Micromedex®. A nested case-control study was conducted to evaluate the associations between inappropriate polypharmacy and ED visits during anti-neoplastic therapy. Multivariate logistic regressions were performed after adjusting for age, sex, cancer diagnosis, prior ED visits, Charlson Comorbidity Index, and type of anti-neoplastic therapy.

Results Inappropriate polypharmacy, its subtype PIMs, geriatric, and chemotherapeutic DDIs were observed in 85.4%, 80.4%, 17.3%, and 37.9% of the 21,956 patients receiving anti-neoplastic therapy, respectively. After adjusting for confounding factors, the presence of inappropriate polypharmacy (adjusted odds ratio (aOR) 2.15, 95% confidence interval (CI) 1.97–2.35), 2 or more PIMs (aOR 1.85, 95% CI 1.68–2.02), 2 or more chemotherapeutic DDIs (aOR 2.88, 95% CI 2.54–3.28), and geriatric DDIs (aOR 1.61, 95% CI 1.43–1.80) increased the likelihood of ED visits during anti-neoplastic therapy.

Conclusion This nationwide study showed that inappropriate polypharmacy was prevalent and increased the risk of ED visits in older patients receiving anti-neoplastic therapy. Study findings suggested a need to implement deprescribing strategies in this population.

Keywords Anti-neoplastic agents · Geriatrics · Inappropriate polypharmacy · Potentially inappropriate medication · Drug interaction · Emergency department

Introduction

Cancer burden among older adults continues to grow worldwide. There were 6.7 million newly diagnosed cancer cases (48% of all cancers) in 2012 and this figure is expected to rise to 14 million by 2035 (60% of all cancers) in adults aged 65 years and over [1]. Cancer management can be more complicated and challenging in older patients as it requires careful consideration and thoughtful approaches during therapy. Older patients with cancer often have multiple chronic comorbidities leading to an increased risk from using numerous medications and subsequently causing negative clinical consequences [2, 3].

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Polypharmacy, commonly defined as the use of five or more medications, has been described as one of the public health challenges in the geriatric population owing to its relationship with increased risk of negative clinical outcomes including adverse drug reactions, non-adherence, falls and fractures, hospitalization, and emergency visits [4]. Polypharmacy may be appropriate or inappropriate, depending on the case. As polypharmacy in patients with multi-morbidity is sometimes necessary and beneficial in some clinical situations [5], distinguishing between appropriate and inappropriate polypharmacy is necessary. Inappropriate polypharmacy is defined as the use of one or more medications that are not needed and the use of medications that expose the patient to a high risk of adverse drug reactions. An unwillingness or inability to take the prescribed medication is also considered inappropriate polypharmacy [6].

The use of potentially inappropriate medications (PIMs) is referred to as inappropriate polypharmacy when the risks outweigh the benefits, especially when safer alternatives are available [7]. The reported prevalence of the use of PIMs in older adults with cancer ranges from 21 to 51% [8]. In addition, the potential drug-drug interactions (DDIs) associated with anti-neoplastic agents could be considered as inappropriate polypharmacy as they render patients vulnerable to the adverse effects of the drug. Previous studies have shown the presence of clinically significant drug interactions in approximately 27–58% of patients who receive anti-neoplastic therapy [9]. Studies also show that patients undergoing treatment with oral targeted anticancer agents are at considerable risk for DDIs [10].

With an increase in the geriatric population undergoing cancer treatment and a growing need for special care, determining the prevalence and consequences of inappropriate polypharmacy in older patients receiving anti-neoplastic therapy would be helpful in addressing the current status of the quality of care, potential risks, and the interventional strategies. However, epidemiological studies regarding these issues remain insufficient as they were mostly conducted in specific cancer patients, patients using specific anti-neoplastic agents, a relatively small sample size, or patients in single institutions [11–13]. Furthermore, only limited studies investigated the association of inappropriate polypharmacy, PIMs, or DDIs, alone or in combinations with negative clinical consequences, which showed inconsistent results in the geriatric oncology population [14–17].

We aimed to investigate the nationwide prevalence and predicting factors of inappropriate polypharmacy comprising PIMs and DDIs, and their association with emergency department (ED) visits in older Korean patients receiving anti-neoplastic therapy.

Methods

Database source and population

We used the 2016 National Adult Patient Sample database obtained from the Korean Health Insurance Review and Assessment Service (HIRA) database, which included 1,327,455 patients corresponding to 20% of the total population older than 65 years. Among them, 28,506 patients were prescribed anticancer drugs. We identified 21,956 patients (77.0 %) who were assigned diagnostic codes for cancer after excluding 6550 patients who received anti-neoplastic agents such as methotrexate, rituximab, and cyclophosphamide for non-cancer disease treatment (Fig. 1). Anticancer drugs were identified using their Anatomical Therapeutic Chemical (ATC) codes and classified into cytotoxic chemotherapy (ATC code L01 except for targeted therapy), targeted therapy, (ATC codes L01XC, L01XE, and some medications belonging to L01XX), and endocrine therapy (ATC code L02). Diagnostic codes for cancer were based on the International Classification of Diseases, 10th edition (ICD-10) including codes C00-C96 (cancer) and D37-D48 (neoplasms of uncertain or unknown behavior, polycythemia vera, and myelodysplastic syndromes). The first date on which an anticancer drug was prescribed in 2016 was defined as the cohort entry date; the last date that was covered by an anticancer drug prescription, or the last day of 2016, whichever was earlier, was defined as the study end date. This study was approved by the Seoul National University institutional review board (SNU 18-09-055).

Definition of outcomes and variables

Inappropriate polypharmacy

We defined inappropriate polypharmacy as a practice involving the use of one or more PIMs or combinations of medications with potential DDIs that should be avoided during anti-neoplastic therapy. The PIMs prescribed during anti-neoplastic therapy were assessed according to the 2019 American Geriatrics Society (AGS) Beers Criteria® for inappropriate use in the geriatric population [18]. The majority of PIMs for this population were included; however, medications that are inappropriate for adults with a specific disease, and those that should be used with caution, were excluded. Additionally, according to the recommendations of the Beers Criteria®, injections of first-generation antihistamines were not classified as PIMs. The prevalence evaluation was based solely on the category of PIM for each patient; hence, we only counted a PIM once when the

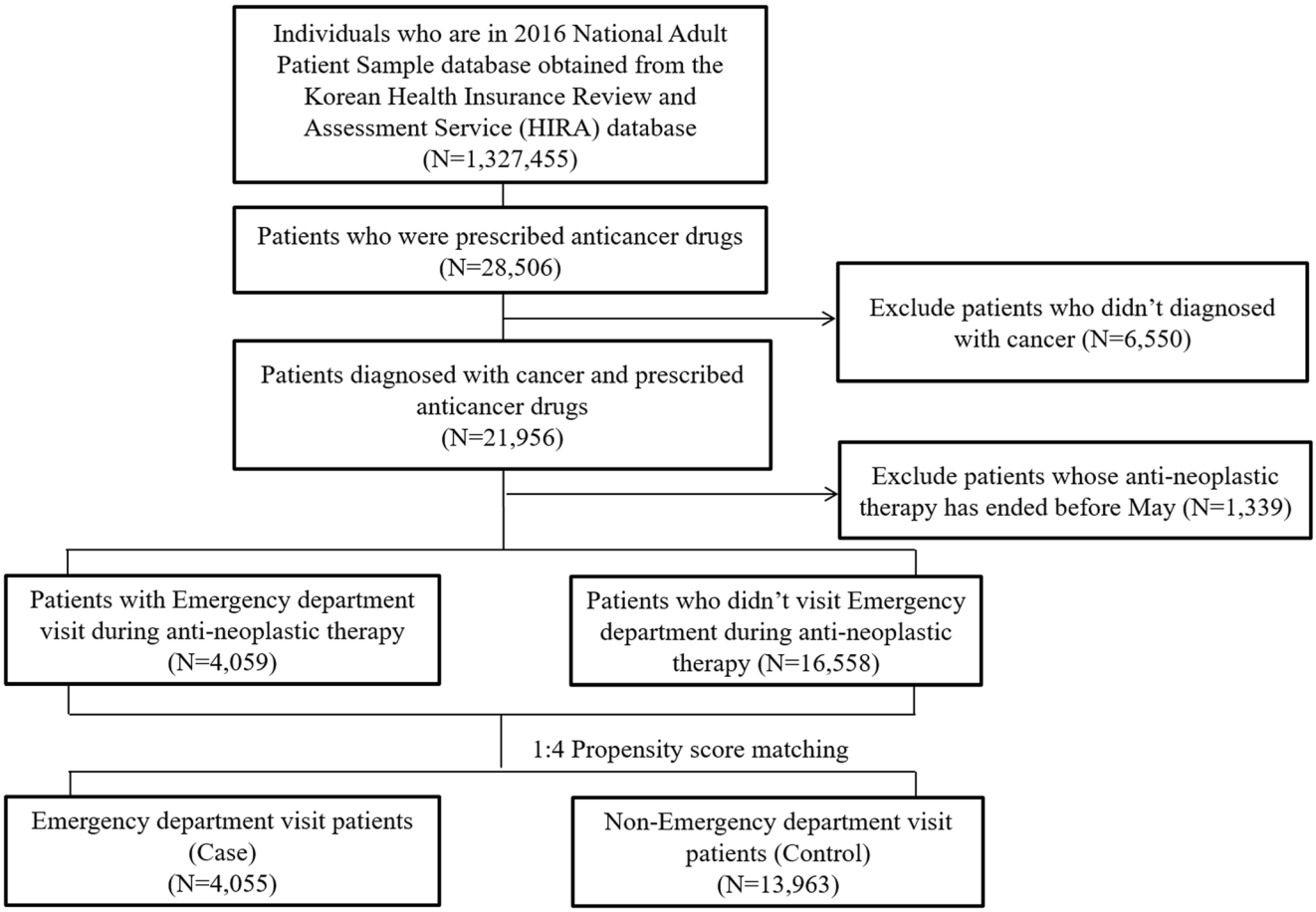

Fig. 1 Flowchart depicting the methodology of patient selection

same type was repeated in individual patients. We also evaluated the prevalence of individual drugs belonging to the same class of PIMs.

To identify clinically significant DDIs that increase the risk of adverse drug reactions, those that should be avoided in the older adults as described in the 2019 AGS Beers Criteria®, namely geriatric DDIs and potentially significant interactions involving anticancer drugs (chemotherapeutic DDIs), based on a reference database, were screened. For chemotherapeutic DDIs, those categorized as "D" or "X" by Lexicomp Online™, or those categorized as "major" or "contraindications" in severity by Micromedex®were included [19].

Inappropriate polypharmacy and emergency department visit

In order to evaluate the clinical impact of inappropriate polypharmacy in older patients with cancer, the associations between inappropriate polypharmacy and ED visits were evaluated using a nested case-control study design. Among the patients who received anti-neoplastic therapy, cases were defined as those with ED visits after May 2016 during anti-neoplastic therapy. Only the first ED visit during the study period was included and the date of the first visit was defined as the index date. Controls were selected from those who did not visit the ED during anti-neoplastic therapy after matching the first date of anti-neoplastic therapy in 2016 (cohort entry date). We excluded patients who stopped anti-neoplastic therapy before May were excluded and only evaluated those who made ED visits during anti-neoplastic therapy (Fig. 1).

The evaluation of the overall practice of inappropriate polypharmacy, number of PIMs, and the presence of geriatric and chemotherapeutic DDIs was based on medications used for more than 5 days during the 1-month period before the index date.

Statistical analysis

Baseline characteristics of the study population were summarized using descriptive statistics. To compare variables between the case and control groups, chi-square statistics were applied. Multivariate logistic regression analysis was performed to investigate the factors associated with inappropriate polypharmacy and the associations between inappropriate polypharmacy and ED visits.

To evaluate the impact of inappropriate polypharmacy on multiple ED visits, we conducted a multinomial logistic regression analysis after categorizing ED visits as no visit, one-time visit, or multiple visits (≥ 2) during anti-neoplastic therapy as a post hoc analysis.

The confounding variables adjusted in this multivariate logistic regression analysis in the identification of predictors for inappropriate polypharmacy were age, sex, insurance, cancer diagnosis, type of anti-neoplastic agents, the Charlson Comorbidity Index (CCI) score, duration of cancer treatment, type of predominantly visited healthcare facilities, frequency of healthcare visits, and the number of prescribers during a 1-year duration. Moreover, age, sex, cancer diagnosis, prior ED visits, CCI score, type of anti-neoplastic therapy, and the number of chronic medications were adjusted in the analysis of the association between inappropriate polypharmacy and ED visits. The number of chronic medications was determined based on the medications that were used at least 20 days a month. Furthermore, we selected the maximum number of concomitant medications as a representative value for a cross-sectional study. Data management and statistical analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Population characteristics

A total of 21,956 patients (1.7%) selected for this study were diagnosed with cancer and prescribed anticancer drugs. The mean age was 74.2 years and 62.6% of the patients were men. Prostate cancer (27.3%) was the most common, followed by breast cancer (16.5%), colon cancer (13.8%), and lung cancer (13.6%). The proportion of patients who received oral and injectable anticancer drugs was 56.2% and 66.9%, respectively. Cytotoxic, endocrine, and targeted drugs were prescribed to 12,652 (52.1%), 8375 (34.5%), and 3277 patients (13.5%), respectively. In general, the duration of anti-neoplastic therapy was over 6 months (54.3%). Polypharmacy and excessive polypharmacy were observed in 69.1% and 26.8% of the patients, respectively (Table 1).

Prevalence and factors associated with inappropriate polypharmacy

Inappropriate polypharmacy was observed in 18,760 patients (85.4%) among those receiving anti-neoplastic therapy. A total of 41,912 cases in 17,642 subjects (80.4%) were prescribed at least one PIM independent of their diagnosis or condition, and 11,634 patients (53.0%) were prescribed two or more PIMs (Table 2). PIMs with strong anticholinergic effects were prescribed to 59.4% of patients, with first-generation oral antihistamines being the most commonly used anticholinergics (40.5%), followed by antispasmodics (9.2%), antidepressants (7.8%), and skeletal muscle relaxants (1.7%). The second most commonly prescribed class of PIM was megestrol (26.2%), followed by benzodiazepines (25.4%), metoclopramide (19.8%), and zolpidem (13.2%) (Supplementary Table 1).

A total of 3806 subjects (17.3%) experienced at least one DDI based on the 2019 AGS Beers Criteria® (Table 2). DDIs were mostly encountered when three or more CNS-active drugs (8.3%), two or more strong anticholinergics (7.5%), opioids with pregabalin or gabapentin (5.2%), opioids with benzodiazepines (3.6%), and corticosteroids with NSAIDs (1.4%) were used (Supplementary Table 2).

DDIs in anti-neoplastic therapy were observed in 37.9% of all patients (Table 2). The number of cases per patient averaged 1.95. The most common oral anticancer drug involved was anagrelide (16.1%), followed by gefitinib (13.1%) and tamoxifen (9.9%). Among the drugs that interacted with oral anticancer drugs, acid suppressants including proton pump inhibitors (15.0%) and H_2 receptor antagonist (13.5%) were the most common. The most common injectable anticancer drugs showing interaction were doxorubicin (26.1%), followed by leuprorelin (23.2%) and cisplatin (18.6%). Furosemide (19.2%) was found to be the most prevalent drug interacting with injectable anticancer drugs (Supplementary Table 3).

Multivariate logistic regression analysis showed that medical aid and national meritorious service, CCI, certain cancer diagnoses, duration of cancer treatment, type of predominately visited healthcare facilities, frequency of healthcare visits, the number of prescribers, and the type of anti-neoplastic agents used in therapy were some factors associated with inappropriate polypharmacy (Table 3). Patients with lymphoma (adjusted odds ratio, aOR 3.53, 95% confidence interval (CI), 2.13–6.23), lung cancer (aOR 2.54, 95% CI 1.94–3.32), and leukemia (aOR 1.62, 95% CI, 1.19–2.22) were more likely to display inappropriate polypharmacy than those with prostate cancer. Patients who were administered anti-neoplastic therapy using only endocrine agents (aOR 0.52, 95% CI 0.42–0.64) or only targeted agents (aOR 0.69, 95% CI 0.57–0.84) were less likely to show inappropriate polypharmacy. Patients who received a combination of cytotoxic and endocrine or targeted agents (aOR 2.75, 95% CI 2.19–3.50) were more likely to show inappropriate polypharmacy than those who were treated with cytotoxic agents only. Cancer treatment for ≥ 6 months increased the likelihood of inappropriate polypharmacy 2.7 times (95% CI 2.43–3.01). Frequency of healthcare visits more than 24 times and the involvement of 6 or more prescribers during the year were found to increase the risk of inappropriate polypharmacy 1.56-fold (95% CI 1.40–1.74) and 1.79-fold (95% CI 1.61–1.98), respectively.

Table 1 Baseline characteristics of patients receiving anti-neoplastic therapy

Characteristics	Cross-sectional study	Nested case-control study		
	Entire cohort (N = 21,956) N (%)	Case (N = 4055) N (%)	Control (N = 13,963) N (%)	p value
Age, mean (± SD), years	74.2 (± 5.7)	74.3 (± 5.9)	74.2 (± 5.8)	0.264
65–74 years	12,174 (55.5)	2233 (55.1)	7768 (55.6)	0.741
75–84 years	8587 (39.1)	1590 (39.2)	5430 (38.9)	
≥ 85 years	1195 (5.4)	232 (5.7)	765 (5.5)	
Sex, male	13,750 (62.6)	2627 (64.8)	8623 (61.8)	< 0.001
Insurance type				0.024
Health insurance	19,603 (89.3)	3576 (88.2)	12,489 (89.4)	
Medical aid and national meritorious service	2353 (10.7)	479 (11.8)	1474 (10.6)	
Charlson Comorbidity Index score				< 0.001
0–3	4970 (22.6)	411 (10.1)	3709 (26.6)	
4–5	5162 (23.5)	757 (18.7)	3472 (24.9)	
≥ 6	11,824 (53.9)	2887 (71.2)	6782 (48.6)	
Cancer diagnosis				
Prostate cancer	5986 (27.3)	981 (24.2)	4015 (28.8)	< 0.001
Breast cancer	3633 (16.5)	374 (9.2)	2718 (19.5)	< 0.001
Colon cancer	3038 (13.8)	667 (16.4)	1814 (13.0)	< 0.001
Lung cancer	2982 (13.6)	804 (19.8)	1568 (11.2)	< 0.001
Gastric cancer	1593 (7.3)	355 (8.8)	914 (6.6)	< 0.001
Leukemia	974 (4.4)	253 (6.2)	544 (3.9)	< 0.001
Lymphoma	695 (3.2)	171 (4.2)	393 (2.8)	< 0.001
Renal cancer	366 (1.7)	87 (2.1)	198 (1.4)	< 0.001
Type of anti-neoplastic agents				
Cytotoxic agents	12,652 (52.1)	2832 (69.8)	7385 (52.9)	< 0.001
Endocrine agents	8375 (34.5)	1089 (26.9)	5975 (42.8)	< 0.001
Targeted agents	3277 (13.5)	824 (20.3)	1880 (13.5)	< 0.001
Formulation of anti-neoplastic agents				
Oral	12,339 (56.2)	1940 (47.8)	8083 (57.9)	< 0.001
Injection	14,694 (66.9)	2662 (65.7)	7721 (55.3)	< 0.001
Duration of cancer treatment				< 0.001
< 30 days	0 (0)	0 (0)	0 (0)	
30–89 days	5534 (25.2)	574 (14.2)	3135 (22.5)	
90–179 days	4489 (20.5)	946 (23.3)	2757 (19.7)	
≥ 180 days	11,933 (54.3)	2535 (62.5)	8071 (57.8)	
Number of chronic medications				< 0.001
< 5	6786 (30.9)	1485 (36.6)	6531 (46.8)	
5–9	9285 (42.3)	1577 (38.9)	5023 (36.0)	
≥ 10	5885 (26.8)	993 (24.5)	2409 (17.3)	

Impact of inappropriate polypharmacy on emergency department visit

Among the 21,956 patients who were prescribed an anticancer drug during the year 2016, 4055 patients (18.5%) who visited the ED after May 1 during anti-neoplastic therapy were identified as study subjects. After performing 1:4 matching with the cohort entry date, 13,963 patients were selected as controls. Age distribution did not significantly differ between case and control cohorts; however, the case cohort included more male patients with a higher CCI score (6 or greater) than the control cohort. As expected, the major baseline characteristics including cancer diagnosis, type of chemotherapeutic drugs, and treatment duration differed significantly between the case and control cohorts (Table 1). After adjusting for confounding factors, it was observed that inappropriate polypharmacy increased the likelihood of ED visits during anti-neoplastic therapy (aOR 2.15, 95% CI 1.97–2.35). Additionally, the use of

Table 2 Prevalence of inappropriate polypharmacy consists of potentially inappropriate medications and drug-drug interactions in older adults receiving anti-neoplastic therapy ($N = 21,956$)

Variables	Number of patients (%)
Inappropriate polypharmacy	18,760 (85.4)
Potentially inappropriate medications	17,642 (80.4)
1	6008 (27.4)
2	4927 (22.4)
≥ 3	6707 (30.5)
Geriatric drug-drug interactions	3806 (17.3)
1	2357 (10.7)
2	917 (4.2)
≥ 3	532 (2.4)
Chemotherapeutic drug-drug interactions	8312 (37.9)
1	4770 (21.7)
≥ 2	3542 (16.1)
Oral anticancer drug	2974 (13.5)
Injectable anticancer drug	5636 (25.7)

two or more PIMs (aOR 1.85, 95% CI 1.68–2.02), one or more geriatric DDIs (aOR 1.61, 95% CI 1.43–1.80), and two or more chemotherapeutic DDIs (aOR 2.88, 95% CI 2.54–3.28) increased the likelihood of visiting the ED during anti-neoplastic therapy (Table 4). Post hoc analysis showed that higher correlations with inappropriate polypharmacy, PIMs, and geriatric DDIs in patients who visited the ED more than once than in those who visited the ED only once (Supplementary Table 4).

Discussion

We demonstrated a high prevalence of inappropriate polypharmacy (85.4%) arising from the use of PIMs and DDIs and showed their strong association with ED visits in older patients receiving anti-neoplastic therapy.

During anti-neoplastic therapy, 80.4% of patients were prescribed more than one PIM, while 53% were prescribed more than two PIMs. The prevalence observed in this study was relatively higher than that noted in previous studies. Previous systematic reviews show that the prevalence of the use of PIMs ranges from 21.3% to 63.0% in the older patients who reside in long-term care facilities [20] and 43.2% in those who are residents of nursing homes [21]. Another study that systematically reviewed the prevalence of PIM in older patients with cancer reports a prevalence of 19.0–52.0% [15]. This discrepancy could be explained by the difference in population, criteria used for assessing PIMs, clinical setting, and sources of databases used for analyses. We used the updated 2019 AGS Beers Criteria®, which could detect the use of more PIMs than the prior version. Since we used nationwide claims data, we captured every prescription from every healthcare facility that showed a high prevalence of PIMs compared with previous studies, most of which were conducted in a single center or in patients with specific cancer [11, 22, 23].

The 2019 AGS Beers Criteria® include megestrol due to its minimal effect on weight despite an increased risk of death [24], and metoclopramide and first-generation antihistamines, which can have extrapyramidal and anticholinergic adverse effects, respectively, in frail older adults. However, these medications are commonly used to promote appetite, manage breakthrough chemotherapy-induced nausea/vomiting, and to prevent or treat the allergic side effects of chemotherapy in patients receiving anti-neoplastic therapy. The prevalence of inappropriate polypharmacy was 58.3% after excluding these three categories. As the AGS Beers Criteria® have been developed for the older population, special consideration is needed to define and determine PIMs for adult patients with cancer.

We analyzed the DDIs in two directions: geriatric DDI and chemotherapeutic DDI. Among the DDIs presented in the 2019 AGS Beers Criteria®, three or more CNS-active drugs showed the highest usage in 8.3% and 7.5% of the patients using two or more anticholinergic agents, respectively, which increased the risk of falls and fractures, cognitive decline, and other anticholinergic adverse effects [25, 26]. This was followed by drug interactions involving opioids. Although DDIs in the geriatric population have not been elucidated in previous studies, the high prevalence of DDIs involving CNS-active drugs was also observed in a previous study [9].

Clinically significant chemotherapeutic DDIs were detected in 37.9% of patients, which were in agreement with the results from previous studies [7, 12]. Similar to a previous study [10], tyrosine kinase inhibitors such as gefitinib or erlotinib combined with acid suppressants comprised most DDIs involving oral anticancer drugs. Among injectable anticancer drugs, doxorubicin was most frequently involved in DDIs. This is because doxorubicin is a substrate of CYP2D6, CYP3A4, and P-glycoprotein; hence, it has many interactions with other drugs that are substrates of these enzymes. It should be noted that this interaction might increase the toxicity of the anticancer agent.

The multivariate logistic regression analysis showed that the presence of inappropriate polypharmacy was likely to increase in patients with high comorbidity, frequent visits of healthcare, and multi-prescribers, and was in accord with predictors identified in the general population [27]. In addition, adult patients with lymphoma, leukemia, and lung cancer had a higher likelihood of inappropriate polypharmacy than those without. This might be partly explained due to the prevalent use of doxorubicin and tyrosine kinase inhibitors, which showed a high potential of DDIs in lymphoma or leukemia and lung cancer, respectively.

Table 3 Multivariate analysis of factors associated with inappropriate polypharmacy in older adults receiving anti-neoplastic therapy ($N = 21,956$)

Factor	Odds ratio (95% CI)	p value
Age		
65–74 years	1	
75–84 years	1.04 (0.95–1.13)	0.431
≥ 85 years	0.86 (0.72–1.01)	0.069
Sex		
Female	1	
Male	0.95 (0.85–1.06)	0.339
Insurance		
Health insurance	1	
Medical aid and National meritorious service	1.34 (1.16–1.55)	< 0.001
Charlson comorbidity index		
< 4	1	
4–5	1.72 (1.55–1.91)	< 0.001
≥ 6	2.72 (2.47–3.00)	< 0.001
Cancer diagnosis		
Prostate cancer	1	
Breast cancer	0.68 (0.61–0.77)	< 0.001
Colon cancer	0.82 (0.64–1.04)	0.104
Gastric cancer	0.67 (0.52–0.87)	0.002
Leukemia	1.62 (1.19–2.22)	0.003
Lung cancer	2.54 (1.94–3.32)	< 0.001
Lymphoma	3.53 (2.13–6.23)	< 0.001
Renal cancer	1.08 (0.69–1.73)	0.739
Others	1.02 (0.82–1.27)	0.847
Type of anti-neoplastic agents		
Cytotoxic agents only	1	
Endocrine agents only	0.52 (0.42–0.64)	< 0.001
Targeted agents only	0.69 (0.57–0.84)	0.001
Mixed anti-neoplastic therapy	2.75 (2.19–3.50)	< 0.001
Duration of cancer treatment		
30–89 days	1	
90–179 days	1.59 (1.42–1.79)	< 0.001
≥ 180 days	2.70 (2.43–3.01)	< 0.001
Type of predominately visited healthcare facilities		
Primary care clinic	1	
Small hospital	0.95 (0.77–1.17)	0.598
General hospital	0.89 (0.80–1.00)	0.049
Tertiary teaching hospital	0.83 (0.75–0.92)	< 0.001
Frequency of healthcare visits during 1 year		
< 24	1	
≥ 24	1.56 (1.40–1.74)	< 0.001
Number of prescribers during 1 year		
< 6	1	
≥ 6	1.79 (1.61–1.98)	< 0.001

In this current study, inappropriate polypharmacy and its subtype of PIMs and DDIs were shown to increase the risk of ED visits during anti-neoplastic therapy. Older patients with inappropriate polypharmacy displayed a 2.15-fold higher risk of ED visits during anti-neoplastic therapy than those without, after adjusting for confounding factors. The association of

Table 4 The association of inappropriate polypharmacy and its subtypes with emergency department visits in older adults receiving anti-neoplastic therapy ($N = 18,018$)

	Number of patients			Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
	Total	Case	Control		
Inappropriate polypharmacy					
0	6914	844	6070	1	1
≥ 1	11,104	3211	7893	2.93 (2.69–3.18)	2.15 (1.97–2.35)
Use of potentially inappropriate medications					
0	8245	1273	6972	1	1
1	4930	1188	3742	1.74 (1.59–1.90)	1.48 (1.34–1.62)
≥ 2	4843	1594	3249	2.69 (2.47–2.92)	1.85 (1.68–2.02)
Geriatric drug-drug interactions					
0	16,257	3469	12,794	1	1
≥ 1	1761	592	1169	1.87 (1.63–2.08)	1.61 (1.43–1.80)
Chemotherapeutic drug-drug interactions					
0	14,187	2574	11,613	1	1
1	2435	850	1585	2.42 (2.20–2.66)	1.97 (1.78–2.19)
≥ 2	1396	631	765	3.72 (3.32–4.17)	2.88 (2.54–3.28)
Number of chronic medications					
0–4	8016	1485	6531	1	1
5–9	6600	1577	5023	1.38 (1.28–1.50)	1.32 (1.21–1.44)
≥ 10	3402	993	2409	1.81 (1.65–1.99)	1.53 (1.38–1.70)

*Adjusted for age, sex, cancer diagnosis, prior ED visits, the Charlson Comorbidity Index, and type of anti-neoplastic therapy

inappropriate polypharmacy with ED visits was stronger than that of excessive polypharmacy defined by the number of chronic medications. The impact of PIMs on clinical outcomes in cancer patients appears to be controversial. In a systematic review studying adverse outcomes (postoperative delirium, length of hospital stay, 30-day postoperative mortality, treatment delay, dose reductions, grade 3–4 toxicity, survival) in the older patients with cancer [15], the association of PIMs with adverse outcomes was investigated in three studies and only one study reported the association of PIMs with ED visits as one of the outcomes [22]. However, a time-to-event analysis fails to show the association of PIM with ED hospitalization and death in patients with breast and colorectal cancer [22].

In a previous study evaluating 301 older Korean patients receiving first-line palliative anti-neoplastic therapy [12], polypharmacy (5 or more medications), but not the use of PIMs, was associated with a higher risk of hospitalization or increased frequency of ED visits during the anti-neoplastic therapy period.

This current study revealed that older patients experiencing two or more DDIs resulting from anti-neoplastic therapy had a 2.88-fold higher risk of ED visits during anti-neoplastic therapy (95% CI 2.54–3.28). These findings might suggest that the negative effects of DDIs, including those induced by chemotherapeutic agents, could be more severe because of the narrow therapeutic index of these chemotherapeutic agents. Moreover, the increased toxicity or loss of efficacy of these agents was a critical factor in cancer treatment. We believe that this is the first report that shows the significant association of potential chemotherapeutic DDI with ED visits in a nationwide cohort.

In addition, we identified a greater association between the use of inappropriate polypharmacy, PIMs and geriatric DDIs, and multiple ED visits than with a one-time ED visit; however, chemotherapeutic DDIs and the number of chronic medications did not show a greater association with multiple ED visits. Although it was difficult to explain these results, the clinician's limited awareness of inappropriate medication use in older patients with cancer could contribute to this association pattern [28]. Hence, the efforts to prevent the use of inappropriate medications are needed in older patients receiving anti-neoplastic therapy.

This study has a few limitations. First, due to the nature of the claims data, we could not include drugs that were not listed in the reimbursement formulary and drugs that were available without a prescription, such as first-generation antihistamines used in common cold. Second, the cases in which physicians may have advised the patients to take medications "as needed," could not be confirmed in this study; this may have contributed to an overestimation of prevalence. Third, we included only PIMs and DDIs for inappropriate polypharmacy. PIMs for patients with a specific disease or condition and those that need to be used with caution, dose effect,

therapeutic class duplication, or unindicated medications could not be analyzed in this report. Additionally, as mentioned above, the most explicit criteria for PIMs were intended for the general older population and validated explicit criteria for PIMs in patients with cancer have not been developed. Fourth, we could not resolve the reason for ED visits and therefore, it was not possible to analyze whether the reason for the ED visits was directly due to inappropriate polypharmacy or not. Lastly, we could not consider factors that were not available in claims data for confounding factors.

Despite these limitations, to our knowledge, this is the first population-based study that shows a high prevalence of inappropriate polypharmacy including the use of PIMs and DDIs and its association with adverse outcomes and ED visits in older patients receiving anti-neoplastic therapy. Based on these findings, a systematic approach for deprescribing medications using methods including sharing the medication history among healthcare professionals, routine medication review by clinical pharmacists, and the development and implementation of computer-based warning systems is essential. This would guide clinicians in accurately prescribing drugs for the geriatric population receiving anti-neoplastic therapy and help reduce the cases of inappropriate polypharmacy.

Conclusions

In this study, we showed that inappropriate polypharmacy was prevalent in older patients receiving anti-neoplastic therapy and significantly increased the risk of ED visits. Our study findings suggested a need to implement deprescribing strategies in the geriatric population.

Authors' contributions Yewon Suh: conceptualization, data curation, formal analysis, writing—original draft preparation. Young-Mi Ah and Eunsook Lee: methodology, validation, writing—review and editing. Ju-Yeun Lee: conceptualization, methodology, supervision, writing—review and editing, funding acquisition.

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Availability of data and material The dataset supporting the conclusions of this article is available from the Korea National Health Insurance Service (KNHIS) Data Sharing Service homepage (https://nhiss.nhis.or.kr/bd/ab/bdaba001cv.do), but restrictions apply to the availability of these data. The KNHIS, the data provider, requires all involved researchers to pledge not to share, release, or review the data with other entities.

Compliance with ethical standards

This study was approved by the Seoul National University institutional review board (SNU 18-09-055).

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, Soerjomataram I (2019) Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer 144(1): 49–58. https://doi.org/10.1002/ijc.31664
2. LeBlanc TW, McNeil MJ, Kamal AH, Currow DC, Abernethy AP (2015) Polypharmacy in patients with advanced cancer and the role of medication discontinuation. Lancet Oncol 16:e333–e341. https://doi.org/10.1016/S1470-2045(15)00080-7
3. Maggiore RJ, Gross CP, Hurria A (2010) Polypharmacy in older adults with cancer. Oncologist 15(5):507–522. https://doi.org/10.1634/theoncologist.2009-0290
4. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK (2014) Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc 62(12):2261–2272. https://doi.org/10.1111/jgs.13153
5. Cadogan CA, Ryan C, Hughes CM (2016) Appropriate polypharmacy and medicine safety: when many is not too many. Drug Saf 39(2):109–116. https://doi.org/10.1007/s40264-015-0378-5
6. World Health Organization (2019) Medication safety in polypharmacy: technical report, World Health Organization
7. Alkan A, Yaşar A, Karcı E, Köksoy EB, Ürün M, Şenler FÇ, Ürün Y, Tuncay G, Ergün H, Akbulut H (2017) Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. Support Care Cancer 25(1):229–236. https://doi.org/10.1007/s00520-016-3409-6
8. Reis CM, Dos Santos AG, de Jesus SP, Reis AMM (2017) Factors associated with the use of potentially inappropriate medications by older adults with cancer. J Geriatric Oncol 8(4):303–307. https://doi.org/10.1016/j.jgo.2017.05.003
9. Van Leeuwen RW, Brundel DH, Neef C, van Gelder T, Mathijssen RH, Burger DM, Jansman FG (2013) Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer 108(5):1071–1078. https://doi.org/10.1038/bjc.2013.48
10. Kim SH, Suh Y, Ah YM, Jun K, Lee JY (2019) Real-world prevalence of potential drug-drug interactions involving oral antineoplastic agents: a population-based study. Support Care Cancer. https://doi.org/10.1007/s00520-019-05204-2
11. Park JW, Roh JL, Lee SW, Kim SB, Choi SH, Nam SY, Kim SY (2016) Effect of polypharmacy and potentially inappropriate medications on treatment and posttreatment courses in elderly patients with head and neck cancer. J Cancer Res Clin Oncol 142(5):1031–1040. https://doi.org/10.1007/s00432-015-2108-x
12. Hong S, Lee JH, Chun EK, Kim KI, Kim JW, Kim SH, Lee YG, Hwang IG, Kim JY, Koh SJ, Ko YH, Shin SH, Woo IS, Kim TY, Baek JY, Kim HJ, Kim HJ, Lee MA, Kwon JH, Hong YS, Ryoo HM, Kim JH (2020) Polypharmacy, inappropriate medication use, and drug interactions in older Korean patients with cancer receiving first-line palliative chemotherapy. Oncologist 25(3):e502–e511. https://doi.org/10.1634/theoncologist.2019-0085
13. Leger DY, Moreau S, Signol N, Fargeas JB, Picat MA, Penot A, Abraham J, Laroche ML, Bordessoule D (2018) Polypharmacy, potentially inappropriate medications and drug-drug interactions in geriatric patients with hematologic malignancy: Observational single-center study of 122 patients. J Geriatric Oncol 9(1):60–67. https://doi.org/10.1016/j.jgo.2017.07.015
14. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM (2016) Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatric Oncol 7(5):346–353. https://doi.org/10.1016/j.jgo.2016.07.010
15. Mohamed MR, Ramsdale E, Loh KP, Arastu A, Xu H, Obrecht S, Castillo D, Sharma M, Holmes HM, Nightingale G, Juba KM,

Mohile SG (2020) Associations of polypharmacy and inappropriate medications with adverse outcomes in older adults with cancer: a systematic review and meta-analysis. Oncologist 25(1):e94–e108. https://doi.org/10.1634/theoncologist.2019-0406

16. Maggiore RJ, Dale W, Gross CP, Feng T, Tew WP, Mohile SG, Owusu C, Klepin HD, Lichtman SM, Gajra A, Ramani R, Katheria V, Zavala L, Hurria A, Cancer, Aging Research G (2014) Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: effect on chemotherapy-related toxicity and hospitalization during treatment. J Am Geriatr Soc 62(8):1505–1512. https://doi.org/10.1111/jgs.12942
17. Sharma M, Holmes HM, Mehta HB, Chen H, Aparasu RR, Shih YT, Giordano SH, Johnson ML (2019) The concomitant use of tyrosine kinase inhibitors and proton pump inhibitors: prevalence, predictors, and impact on survival and discontinuation of therapy in older adults with cancer. Cancer 125(7):1155–1162. https://doi.org/10.1002/cncr.31917
18. Fick DM, Semla TP, Steinman M, Beizer J, Brandt N, Dombrowski R, DuBeau CE, Pezzullo L, Epplin JJ, Flanagan N, Morden E, Hanlon J, Hollmann P, Laird R, Linnebur S, Sandhu S (2019) American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 67(4):674–694. https://doi.org/10.1111/jgs.15767
19. Seulki An J-YL, Young-Mi A (2020) Evaluation of information consistency of clinically significant drug interactions in tyrosine kinase inhibitors. Korean J Clin Pharm 30(1):44–50. https://doi.org/10.24304/kjcp.2020.30.1.44
20. Storms H, Marquet K, Aertgeerts B, Claes N (2017) Prevalence of inappropriate medication use in residential long-term care facilities for the elderly: a systematic review. Eur J Gen Pract 23(1):69–77. https://doi.org/10.1080/13814788.2017.1288211
21. Morin L, Laroche ML, Texier G, Johnell K (2016) Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. J Am Med Dir Assoc 17(9):862.e861–862.e869. https://doi.org/10.1016/j.jamda.2016.06.011
22. Karuturi MS, Holmes HM, Lei X, Johnson M, Barcenas CH, Cantor SB, Gallick GE, Bast RC Jr, Giordano SH (2018) Potentially inappropriate medication use in older patients with breast and colorectal cancer. Cancer 124(14):3000–3007. https://doi.org/10.1002/cncr.31403
23. Chiang LY, Liu J, Flood KL, Carroll MB, Piccirillo JF, Stark S, Wang A, Wildes TM (2015) Geriatric assessment as predictors of hospital readmission in older adults with cancer. J Geriatric Oncol 6(4):254–261. https://doi.org/10.1016/j.jgo.2015.04.003
24. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S (2013) Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database Syst Rev 2013(3):CD004310. https://doi.org/10.1002/14651858.CD004310.pub3
25. Hanlon JT, Boudreau RM, Roumani YF, Newman AB, Ruby CM, Wright RM, Hilmer SN, Shorr RI, Bauer DC, Simonsick EM, Studenski SA (2009) Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. J Gerontol A Biol Sci Med Sci 64(4):492–498. https://doi.org/10.1093/gerona/gln043
26. Gerretsen P, Pollock BG (2011) Drugs with anticholinergic properties: a current perspective on use and safety. Expert Opin Drug Saf 10(5):751–765. https://doi.org/10.1517/14740338.2011.579899
27. Jun K, Ah YM, Hwang S, Chung JE, Lee JY (2020) Prevalence of anticholinergic burden and risk factors amongst the older population: analysis of insurance claims data of Korean patients. Int J Clin Pharm 42(2):453–461. https://doi.org/10.1007/s11096-020-01010-7
28. Wawruch M, Zikavska M, Wsolova L, Jezova D, Fialova D, Kunzo M, Kuzelova M, Lassanova M, Kruty P, Kriska M (2006) Perception of potentially inappropriate medication in elderly patients by Slovak physicians. Pharmacoepidemiol Drug Saf 15(11):829–834. https://doi.org/10.1002/pds.1290