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Drug-related Problems in Elderly Patients with Hematologic Malignancies: A Single-center Study on Inappropriate Medication Use and Drug-drug Interactions

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ABSTRACT

Aim: Medication-related issues are prevalent among elderly patients diagnosed with hematological malignancies. The present study aimed to evaluate the prevalence and characteristics of polypharmacy, potentially inappropriate medication use (PIM), and drug-drug interactions (DDI) among patients with polypharmacy.

Methods: This cross-sectional study included elderly patients (≥65 years) with hematological malignancies who attended a geriatric outpatient clinic between April and September 2024. Sociodemographic data, medical history, medication use, and chemotherapy status were collected from electronic records. Polypharmacy, PIM, and the DDI were analyzed. PIM was evaluated using the Turkish Elderly Inappropriate Medication (TIME) criteria, whereas the DDI was classified according to the Lexi-Interact database.

Results: In an analysis of 219 patients (mean age 73.9±6.0), 27.8% (n=61) had received chemotherapy. Polypharmacy was observed in 64.4% (n=141) of patients, rising to 70.5% (n=43) in the chemotherapy group. PIM was listed in 63.0% (n=138) of patients, with 77.1% (n=185) of PIMs based on TIME-to-STOP criteria and 22.9% (n=55) on TIME-to-START. Antihypertensives and proton pump inhibitors were most frequently discontinued, whereas calcium and vitamin D were most commonly initiated. DDIs were detected in 73.1% (n=160) of the patients, and 21.9% had at least one major DDI.

Conclusion: Polypharmacy, PIM, and DDI are common in elderly patients with hematological malignancies. The prominence of specific drug groups in inappropriate use and the significant occurrence of major DDIs highlight the need for careful medication management in this population.

Keywords: Hematological malignancy, geriatric patient, polypharmacy inappropriate medication use, drug-drug interactions

Introduction

Hematological malignancies are more common in elderly individuals, and this group also has an important role in the prevalence of cancer. The decrease in physiological reserves with age, increase in comorbidities and pharmacokinetic-pharmacodynamic changes make the treatment process more complicated. In patients with hematological malignancies, the use of multiple drugs because of both the existing malignancy and other chronic diseases is common [1,2]. As expected, drug-related problems, such as polypharmacy, potential inappropriate medication (PIM), and drug-drug interactions (DDI), are more prominent in this patient group [3-5].

Polypharmacy refers to the simultaneous use of 5 or more drugs and is more common in elderly patients and makes clinical patient management difficult [6]. Studies have shown that polypharmacy in geriatric patients is closely associated with adverse outcomes, such as side effects, drug incompatibilities, and clinical complications [7]. The frequency of polypharmacy, especially in patients with hematological malignancies, increases due to the nature of the treatment.

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This may increase the risk of PIM use and DDI in vulnerable patients, leading to increased incidence of adverse drug events, hospitalization, and mortality [8,9].

Polypharmacy does not always indicate inappropriate medication use. PIM encompasses multiple problems, such as medication use without a valid reason, failure to prescribe needed medications, and ineffective doses of appropriate medications [10]. Various tools have been developed to assess PIM. These tools, which include criteria for the need to discontinue and/or start medication, such as the STOPP/START, Beers, and Turkish Elderly Inappropriate Medication (TIME) criteria, provide a comprehensive set of recommendations for inappropriate medication use [11-13]. PIM is common among patients with cancer, including those with hematological malignancies, and some studies have reported prevalence rates as high as 50% (39.9-54%) [3,14,15]. In addition, polypharmacy is associated with DDIs associated with drug toxicity, treatment failure, morbidity, and mortality. Various online tools are used to guide the clinical significance of interactions and predict potential adverse effects by comprehensively assessing DDIs [16-18]. DDIs, which occur when one drug affects the pharmacokinetics or pharmacodynamics of another, are common among patients with hematologic malignancies because of complex treatment regimens that include chemotherapy agents, supportive care medications, and medications for preexisting conditions [5,19]. This study aimed to provide a comprehensive understanding of drug-related problems commonly encountered in this patient population by evaluating polypharmacy, PIMs, and DDIs in elderly patients with hematologic malignancies. The findings will provide guidance for identifying high-risk drug groups and clinically significant interactions that should be considered in clinical practice.

Methods

Study Design

This cross-sectional study included adults aged 65 years and older who were registered in a tertiary outpatient geriatric clinic. Between April 2024 and September 2024, 492 patients with hematological malignancies were admitted to the outpatient clinic. Among these patients, those with advanced dementia, delirium, severe metabolic disorder, sensory disability, communication limitation, and nursing home stay were excluded from the study. Informed consent forms were obtained from all participants, and 219 patients who volunteered to participate in the study were included in the study. This study was conducted in accordance with the Declaration of Helsinki, and the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee approved the study (no: 2024-03/27, date: 14.03.2024).

Assessment of Medications

All prescription and non-prescription medications used by the patients were evaluated and recorded in detail. Polypharmacy was defined as the use of 5 or more drugs, and hyper-polypharmacy was defined as the use of 10 or more drugs [6,20]. PIM was defined by a geriatrician using the TIME criteria determined based on national and international guidelines. TIME criteria is a tool defined in 2020, including 112 criteria for drug discontinuation (TIME-to-STOP) and 41 criteria for drug initiation (TIME-to-START). Although the relevant criteria tool included the nutrition and vaccination sections in addition to medication in patient evaluations, they were not included in the numerical results in the drug initiation and discontinuation evaluation during the analysis. In the DDI evaluation, the Lexi-Interact tool, which provides a comprehensive database to determine the clinical importance and management of interactions, was used [21]. The severity of DDIs was also categorized into risk classes as minor, moderate, and major in accordance with this tool [21].

Patient Characteristics

The participants' age, gender, body mass index, and current diseases were recorded. The patient's hematological malignancy diagnosis was noted by evaluating the patient's history, electronic records, and diagnostic codes. Other accompanying comorbid diseases (hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease and hypothyroidism) were recorded. The presence of 2 or more diseases other than malignancy was defined as multimorbidity [22]. The estimated glomerular filtration rate (eGFR) was evaluated using the Modification of Diet in Renal Disease formula, and patients with a value <60 mL/minute/1.73 m^2 were additionally determined. The functional performances of the patients were evaluated using the Katz Activities of Daily Living Scale [23]. Six points were categorized as full function, 3-5 points as moderate impairment and 1-2 points as severe impairment [23].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., IL, Chicago, U.S.). The numerical variables comprise absolute numbers and percentages, average standard deviation, and median (minimum-maximum). The Student's t-test or the Mann-Whitney U test was used for continuous data comparison. The Kolmogorov-Smirnov test was used to analyze data distribution. The comparison of categorical variables was conducted using the chi-square test. A statistically significant result was accepted when the p value was less than 0.05.

Results

Baseline Characteristics

A total of 219 patients with hematological malignancies were included in the study. The mean age of the participants was 73.9 (±6.0) years, and 55.3% were male. The most common malignancies were multiple myeloma (19.2%), non-Hodgkin lymphoma (15.1%), and chronic lymphoid leukemia (11.9%). The most common comorbidity was hypertension (57.1%),

followed by cardiovascular disease (34.2%) and diabetes mellitus (23.7%). More than half of the patients (64.8%) were functionally fully independent. Of the total patient population, 27.8% (61 individuals) were undergoing chemotherapy at the time of the study. The detailed characteristics of the patient groups that received and did not receive chemotherapy are presented in Table 1.

Medication Properties

In total, 1,327 medications from all patients were evaluated. The median number of medications used by the patients was 6 (0-18) and all patients except 4 were using at least 1 medication. More than half of the patients (64.4%) had polypharmacy and 35 (16.0%) had hyper-polypharmacy. Polypharmacy was more common in those receiving chemotherapy (70.5%), and the rate of hyper-polypharmacy was approximately 2 times higher in the chemotherapy group than in those not receiving chemotherapy (12.7 vs. 24.6) (Table 2). Forty-seven (77.0%) of the patients in this group were using prophylactic treatments because they were receiving chemotherapy, and the median number of prophylactic medications used was 2 (0-4). A total of 63.0% of the patients (138 individuals) were using one or

Table 1. Comparison of baseline sociodemographic and clinical characteristics according to chemotherapy status

Variables	Total (n=219)	Not receiving chemotherapy (n=158)	Receiving chemotherapy (n=61)	p value
Age > years, mean (SD)	73.9 (6.0)	74.2 (5.8)	72.6 (6.2)	0.080
Age group, n (%)				
65-74	128 (58.4)	92 (58.2)	36 (59.0)	0.628
75-84	82 (37.4)	58 (36.7)	24 (39.3)	
≥85	9 (4.1)	8 (5.1)	1 (1.6)	
Sex, male, n (%)	121 (55.3)	86 (54.4)	35 (57.4)	0.762
BMI, mean, mean (SD)	26.9 (5.0)	27.01 (4.9)	26.4 (5.3)	0.523
Hematologic malignancies, n (%)				
Myeloma and plasma cell dyscrasia	42 (19.2)	21 (13.3)	21 (34.4)	**0.024**
Hodgkin lymphoma	6 (2.7)	4 (2.5)	2 (3.3)	
Non-Hodgkin's lymphoma	33 (15.1)	24 (15.2)	9 (14.8)	
Acute myeloid leukemia	12 (5.5)	2 (1.3)	10 (16.4)	
Chronic myeloid leukemia	8 (3.7)	5 (3.2)	3 (4.9)	
Chronic lymphoid leukemia	26 (11.9)	21 (13.3)	5 (8.2)	
Myelodysplastic syndrome	12 (5.5)	9 (5.7)	3 (4.9)	
Other	80 (36.5)	72 (45.6)	8 (13.1)	
Comorbidities, n (%)				
Hypertension	125 (57.1)	94 (59.5)	31 (50.8)	0.287
Diabetes mellitus	52 (23.7)	39 (24.7)	13 (21.3)	0.724
Cardiovascular disease	75 (34.2)	55 (34.8)	20 (32.8)	0.874
Chronic obstructive pulmonary disease	16 (7.3)	13 (8.2)	3 (4.9)	0.565
Cerebrovascular disease	3 (1.4)	2 (1.3)	1 (1.6)	0.831
Hypothyroidism	26 (11.9)	21 (13.3)	5 (8.2)	0.358
Number of comorbidities, *median (range)	2 (0-7)	2 (0-7)	1 (0-4)	**0.014**
Multimorbidity, n (%)	141 (64.4)	111 (70.3)	30 (49.2)	**0.005**
eGFR <60, n (%)	17 (7.8)	11 (7.0)	6 (9.8)	0.574
Katz ADL score, mean (SD)	5.39 (1.08)	5.49 (0.9)	5.11 (1.3)	0.046
Functional category, n (%)				
Full function	142 (64.8)	108 (68.4)	34 (55.7)	0.061
Moderate impairment	68 (31.1)	45 (28.5)	23 (37.7)	
Severe impairment	9 (4.1)	5 (3.2)	4 (6.6)	

Values with p<0.05 are indicated in bold.
*Excluding hematologic malignancy.
ADL: Activities of daily living, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, SD: Standard deviation

Table 2. Evaluation of drug-related characteristics according to chemotherapy status

Variables	Total (n=219), n (%)	Not receiving chemotherapy (n=158), n (%)	Receiving chemotherapy (n=61), n (%)
Number of medications	6 (0-18)	5 (0-16)	7 (1-18)
None	4 (1.8)	4 (0.6)	0 (0.0)
≥1	215 (98.2)	154 (99.4)	61 (100)
≥5	141 (64.4)	98 (62.0)	43 (70.5)
≥10	35 (16.0)	20 (12.7)	15 (24.6)
Number of PIM[†]	1 (0-7)	1 (0-7)	1 (0-5)
PIM use			
None	81 (37.0)	58 (36.7)	23 (37.7)
≥1	138 (63.0)	100 (63.3)	38 (62.3)
Number of total PIMs	240	189	51
TIME-to-STOP	185	141	44
TIME-to-START	55	36	19
DDI			
Number of DDI[†]	2 (0-27)	2 (0-24)	3 (0-27)
None	59 (26.9)	47 (29.7)	12 (19.7)
≥1	160 (73.1)	111 (70.3)	49 (80.3)
Number of total DDIs	939	651	288
Severity of the DDI			
None	9	2	7
Minor	158	96	62
Moderate	692	497	195
Major	80	56	24

[*]Excluding chemotherapeutic agents, [†]median (range).
ADL: Activities of daily living, DDI: Drug-drug interaction, PIM: Potentially inappropriate medication, TIME: Turkish Elderly Inappropriate Medication

more PIMs. Of the 240 PIMs detected in the entire group, 185 (77.1%) were listed as requiring drug discontinuation (TIME-to-STOP) and 55 (22.9%) were listed as requiring drug initiation (TIME-to-START) (Table 2). When evaluated as sections, according to TIME-to-STOP, the most frequent discontinuations were those that met cardiovascular system (A) criteria (n=46, 24.9%), followed by central nervous system (B, n=37, 20.0%) and endocrine system (G, n=26, 14.1%) drugs. According to TIME-to-START, the most frequently started drugs were musculoskeletal system and analgesic group (E) drugs (n=38, 69.1%), followed by cardiovascular system (A, n=9, 16.4%) and central nervous system (B, n=6). The most frequently stopped drugs were antihypertensive drugs in patients with inappropriately tight blood pressure control (A11, n=27), followed by patients with inappropriate proton pump inhibitor (PPI) addition due to multiple drug use (C5, n=21). The most frequently started drugs were Ca and vitamin D preparations in patients with inadequate dietary intake (E1, n=28), followed by the necessity of starting anti-resorptive or anabolic agents in patients with documented osteoporosis (E2, n=10) (Figure 1). Although proportionally more drugs were stopped in the group that did not receive chemotherapy, more drugs were started in the group that received chemotherapy. On the other hand, in both groups, the most frequently intervened drug groups remained unchanged (Figure 1). The median number of DDIs was 2, and only 26.9% (n=59) of patients did not list any drug interactions with Lexi-interact. At least 1 DDI was detected in 73.1% of patients, and this rate was even higher in patients receiving chemotherapy (80.3%). In total, 939 drug interactions were identified with the relevant vehicle. Of the listed interactions, the most frequently detected interaction was level C interaction (n=687, 73.2%), indicating that the relevant interaction may be clinically significant and that careful monitoring and dosage adjustments should be made if necessary (Figure 2). The majority of the interaction severities were at the "moderate" level (n=692), which is defined as "may require medical intervention", while 80 (8.5%) of these interactions were at the major level (potentially leading to serious outcomes such as treatment failure, hospitalization, permanent damage, or death). The number of patients with at least one major DDI was 48 (21.9%). Other evaluations of the drug properties are presented in Table 2.

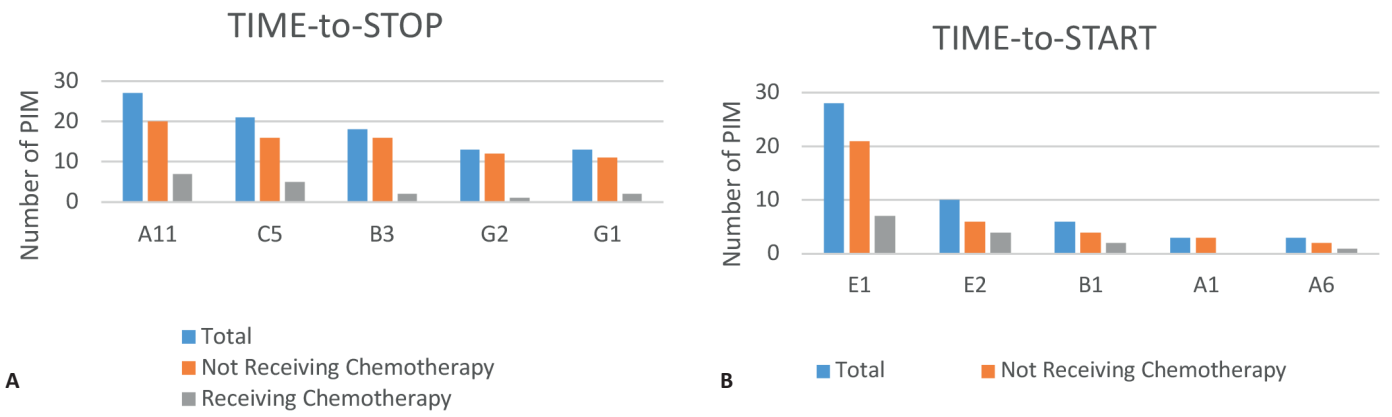

Figure 1. A, B) The five most commonly identified potentially inappropriate medications based on TIME criteria
EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, MI: Myocardial infarction, PIM: Potentially inappropriate medication, PPIs: Proton pump inhibitors, TIA: Transient ischemic attack, SSRIs: Selective serotonin reuptake inhibitors, Na: Sodium, TIME: Turkish Elderly Inappropriate Medication

A11. Strict blood pressure control (<140/90 mmHg) in patients with orthostatic hypotension, cognitive impairment (e.g. dementia) / functional limitation/low life expectancy (<2 years) / high risk of falling.
B3. SSRIs with current or recent significant hyponatremia i.e. serum Na <130 mEq/L (risk of intensifying or precipitating hyponatremia).
C5. PPIs for multiple indications (no benefit, potential harm).
G1. Intensive glycemic control (HbA1c <7%) in patients with limited life expectancy (<5 years) or a history of falls or cognitive impairment.
G2. Metformin if eGFR <30 mL/min/1.73 m^2 (risk of lactic acidosis).
A1. Antiplatelet therapy (aspirin or clopidogrel) for secondary prevention in patients with documented atherosclerotic coronary artery disease (previous acute coronary syndrome/coronary artery angioplasty or stenting/coronary artery bypass grafting/abdominal aortic aneurysm), documented atherosclerotic cerebrovascular disease (presence of ischemic stroke/TIA/previous carotid endarterectomy or stenting) or symptomatic lower extremity artery disease.
A6. Beta-blockers for ischemic heart disease (antianginal effect in chronic ischemic heart disease/mortality reduction effect in post-MI era) or systolic heart failure (EF<=40%) (bisoprolol/prolonged release metoprolol succinate/carvedilol/nebivolol in systolic heart failure; any beta blocker in ischemic heart disease).
B1. Antidepressant treatment in patients with major depressive disorder.
E1. Bone anti-resorptive (bisphosphonate, denosumab) or anabolic therapy (parathormone analog) in patients with documented osteoporosis [fragility fracture and/or bone mineral density T-scores (femur total, femoral neck or total lumbar) <-2.5].
E2. Bisphosphonates in patients who started long-term systemic corticosteroid therapy (an anticipated duration of ≥3 months): i) if >=7.5 mg/day prednisolone or equivalent dose is given, ii) at any dose if T score is <-1.

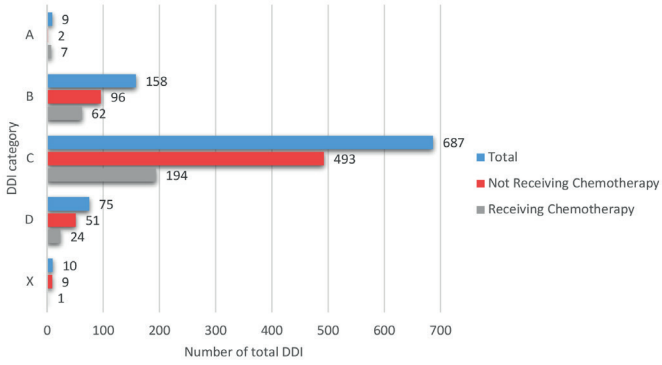

Figure 2. Drug-drug interaction numbers by categories
DDI: Drug-drug interaction, A: No known interaction, B: Action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination

Discussion

Our cross-sectional and descriptive cohort study examined the characteristics of medication use in detail in terms of polypharmacy, PIM use and DDI in elderly individuals with geriatric hematological malignancies. When the frequency of hematological malignancies was evaluated in our study, it was found to be largely consistent with studies conducted for patients of similar ages [23,24]. The median number of drug use was 6 (0-18), and polypharmacy was detected in 64.4%. When studies in the literature were examined, the average number of drugs was found to be between 3 and 10, whereas the frequency of polypharmacy was found to be between 32% and 80%, similar to our study [1,9,25]. The fact that the polypharmacy rate was higher in patients receiving chemotherapy and the hyper-polypharmacy rate was approximately 2-fold higher compared with the other groups can be attributed to the necessity of additional drugs for the management of supportive treatments and side effects used due to the nature of cancer treatment. In particular, antiemetics, opioids, or non-steroidal anti-inflammatory drugs for pain management, gastrointestinal system protectors, antibiotic or antifungal prophylaxis against infection risk, and growth factors used to manage hematological toxicities are frequently added to the treatment [26,27]. The fact that

the rate of prophylactic drug use in this group who received chemotherapy in our study was 77.0% supports this finding. This multidrug use, which is more notable in individuals receiving chemotherapy but is detected in the entire patient population, increases the risks of treatment-related complications and drug interactions, indicating that a more careful approach to patient management is required.

Polypharmacy is not always synonymous with PIM. In patients with hematological malignancies, the use of several medications is necessary not only for malignancy treatment and management but also for patients with past comorbidities. However, striking a balance between necessary and inappropriate medication use is of great importance, especially in the elderly population. In our study, at least one PIM use was detected in approximately two out of every three patients (63.0%). This rate was observed to be higher when compared with studies in the literature, both in the general elderly population and in the limited number of studies on elderly patients with hematological malignancies [3,28]. This increase in PIM rates could be attributed to methodological differences in the assessment tools used for PIM detection and the effects of the malignancy-specific medication burden. The vast majority of these PIMs (77.1%) indicated medication discontinuation (TIME-to-STOP), and this necessity was seen to be particularly prominent among cardiovascular system medications. Discontinuation of antihypertensive medications was the most common intervention. Age-related physiological changes, effects of malignancy, and drugs used during treatment may affect blood pressure or cause drug interactions, resulting in unnecessary drug use in this area [29-31]. In addition, since blood pressure targets adapted to physical performance are in question in elderly patient practice [32], and this is especially taken into consideration by a geriatrician's evaluation, this drug group may have come to the forefront as a PIM. Another group of drugs that should be discontinued is inappropriate PPIs added to the treatment of patients using multiple drugs. Since long-term use of PPIs in elderly patients may lead to various negative outcomes, such as vitamin and mineral deficiencies, increased risk of gastrointestinal infection, and deterioration in renal function, it is important to carefully evaluate the use of these drugs [33,34]. On the other hand, drugs that are considered appropriate to start according to TIME-to-START among PIMs are frequently included in the "Musculoskeletal System and Analgesics" group, and the most needed ones were calcium (Ca) and vitamin D preparations (69.1%). These drugs were followed by agents that should be initiated for osteoporosis treatment. This situation may be associated with both nutritional problems and hematological malignancies in the relevant patient group, and the agents used in the treatment of these malignancies affect Ca and vitamin D metabolism and reduce bone mineral density [35,36]. These findings emphasize the need for a more careful evaluation and regular drug review during the treatment process regarding PIM use, which is frequently observed in elderly patients with hematological malignancies. Correct management of this fine line between polypharmacy and inappropriate drug use can improve patients' quality of life and minimize the risk of complications.

DDI are an important clinical problem in elderly patients with hematological malignancies. In our study, at least one DDI was detected in 73.1% of patients. In another study conducted on 122 elderly patients with hematological malignancies, although a different methodology was used to determine the DDI, the rate was found to be similar to that of our study (71.3%) [3]. DDI rates were higher among patients receiving chemotherapy (80.3%), as expected. Although chemotherapy agents were not included in drug interactions in our study, agents used for prophylaxis and management of secondary side effects of treatment in this patient group can be considered highly responsible for these interactions. The fact that most of the DDIs in our study were in category C (73.2%) indicates that there are risks in the concomitant use of these drugs, but they are clinically manageable. In such cases, potential adverse effects can be prevented with regular monitoring and dose adjustments. Moderate interactions detected in most patients who require medical intervention are not as serious as major interactions. One of the striking findings of our study is that 8.5% of the DDIs were at the major level, and at least one major interaction was found in almost one in every five patients. Major interactions can reduce treatment efficacy or increase toxicity and have the potential to cause serious adverse outcomes, such as hospitalization or death. Therefore, early detection of such interactions in patients with geriatric hematological malignancies and meticulous monitoring and management during the treatment process are of vital importance.

Study Limitations

This study has some important strengths and limitations. First, having a cross-sectional design limits the full revealing of causal relationships. In addition, the fact that the data were obtained from a single center and only from patients who applied to the outpatient clinic limits the generalizability of the results to a large population. Although our sample size is consistent with similar studies in the literature, the variety of malignancy diagnoses and stages prevented the comparability of drug use behaviors among different subgroups and did not allow for more information on this subject. In addition, although there are alternatives to the tools used for the definition of PIM and DDI in our study, it should be considered that some drug-related problems that may be listed in other tools may not have been identified in this analysis. However, our study provides important data that can guide clinical decisions for this population by focusing on the use and management of drugs in elderly patients with hematological malignancies. By making evaluations based on real-world data, inferences for clinical practice have become more meaningful. Considering the limited number of studies on medication management in elderly patients with hematological malignancies, this study can make significant contributions to the existing literature and form the basis for more comprehensive studies to be conducted in the future.

Conclusion

Our study demonstrated the prevalence of medication-related problems, such as polypharmacy, PIM, and DDI, in elderly patients with hematological malignancies. In particular, certain medications were found to be responsible for a significant portion of medication-related problems in this patient group. These findings suggest that regular medication review and the implementation of evidence-based medication management protocols can play critical roles in preventing potential adverse effects and complications. In the future, larger-scale prospective studies are needed to evaluate the effects of medication-related problems on long-term patient outcomes.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee approved the study (no: 2024-03/27, date: 14.03.2024).

Informed Consent: Informed consent forms were obtained from all participants, and 219 patients who volunteered to participate in the study were included in the study.

Footnotes

Authorship Contributions

Concept: N.K.S., B.U.U., Design: N.K.S., B.U.U., Data Collection or Processing: N.K.S., Analysis or Interpretation: B.U.U., Literature Search: N.K.S., B.U.U., Writing: N.K.S., B.U.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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