Potentially Inappropriate Medication Use in Geriatric Oncology Patients: Current Status and Management Strategies (Postprint)

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Abstract

A growing body of research has demonstrated that potentially inappropriate medication (PIM) is prevalent among older adult cancer patients, and compared with the general elderly population, the incidence of PIM may be higher in this patient group, exerting adverse effects on prognosis. Therefore, it is necessary to systematically and comprehensively summarize and analyze existing studies to provide support and reference for future research. This article systematically searched PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Data Knowledge Service Platform to summarize and analyze the screening tools for PIM in cancer patients, the incidence of PIM, the primary medication classes involved, risk factors, and the relationship between PIM and various adverse outcomes. Studies have shown that different PIM screening tools yield varying results when investigating the incidence of PIM in older adult cancer patients, while the list of supportive care medications to be used with caution in older adult patients provided in the NCCN Clinical Practice Guidelines: Older Adult Oncology (2020.v2) demonstrates advantages in providing individualized medication management for cancer patients. Polypharmacy, age, and comorbidities are significantly associated with the occurrence of PIM, and benzodiazepines and analgesics are high-risk medications frequently used by cancer patients. Older adult cancer patients with PIM may have higher rates of mortality, drug-drug interactions, adverse events, emergency department visits, and hospital readmissions. It is hoped that this article will provide a reference for domestic research related to PIM in older adult cancer patients and support the promotion of safe and rational medication use in this population.

Full Text

Preamble

Current Situation of Potentially Inappropriate Medication in Older Cancer Patients and Strategies to Address It

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Abstract An increasing number of studies have demonstrated that potentially inappropriate medication (PIM) occurs commonly in elderly cancer patients, with a higher prevalence than in the general elderly population, which may lead to adverse effects on patient prognosis. Therefore, it is necessary to conduct a systematic and comprehensive review of previous studies to provide support and reference for future research. PubMed, CNKI, and Wanfang Data were systematically searched to summarize and analyze PIM screening tools, PIM prevalence, main drugs involved, influencing factors, and the relationship between PIM and adverse outcomes. The results showed that the prevalence of PIM varied when different screening tools were used in older cancer patients, and the list of supportive care medications requiring caution in older patients provided by the NCCN Clinical Practice Guidelines in Oncology: Older Adult (2020.v2) demonstrated advantages in providing individualized medication management for elderly cancer patients. Polypharmacy, age, and comorbidities were significantly associated with PIM occurrence. Benzodiazepines and analgesics were commonly used high-risk drugs in cancer patients. Elderly cancer patients with PIM may have higher rates of mortality, drug interactions, adverse events, emergency visits, and hospital readmissions. It is hoped that this article will provide a reference for conducting PIM-related research in elderly cancer patients in China and support the promotion of safe and rational medication use in this population.

[**Key words**] Potentially inappropriate medication; Polypharmacy; Cancer patients; Aged; Adverse outcomes

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Introduction

Cancer represents a major public health challenge, with incidence and mortality increasing with age. According to statistics, in 2022, there were 2.79 million

new cancer cases and 1.94 million cancer deaths among older adults in China, accounting for 55.8% and 68.2% of all cancer incidence and mortality, respectively [1]. Due to population aging and increased life expectancy, the number of elderly cancer patients is gradually increasing, placing a substantial burden on healthcare systems.

Elderly cancer patients typically require multiple medications for cancer treatment and supportive care. Additionally, the presence of geriatric comorbidities further increases the number of medications used, leading to an increased risk of polypharmacy (generally defined as taking $ $5 medications daily) in this population [2]. Currently, polypharmacy is prevalent among elderly cancer patients [2], which significantly increases their risk of adverse drug events [3]. Numerous studies have also demonstrated that polypharmacy is an independent risk factor for potentially inappropriate medication (PIM) [4]. PIM refers to medications for which effectiveness has not been established and/or the risk of adverse events exceeds the expected clinical benefit, while safer alternatives are lacking [5].

Current tools for assessing PIM include the Chinese Criteria for Potentially Inappropriate Medication Use in Older Adults (2017 Edition) [6], the 2023 American Geriatrics Society Beers Criteria (AGS Beers Criteria) [7], the 2014 Screening Tool of Older People's Prescriptions (STOPP)/Screening Tool to Alert to Right Treatment (START) [8], and the Medication Appropriateness Index (MAI) [9-10]. However, due to the unique nature of cancer treatment, whether these criteria are equally applicable to elderly cancer patients requires further investigation. Additionally, foreign studies have suggested that PIM is significantly associated with all-cause mortality in elderly cancer populations [2]. However, domestic research on the impact of PIM on prognosis in elderly cancer patients remains scarce.

This article summarizes previous studies on PIM in elderly cancer patients, systematically reviewing the characteristics of different criteria when applied to cancer populations, the prevalence of PIM in elderly cancer patients, risk factors for PIM occurrence, and the main drugs involved. We also analyze the impact of PIM on outcomes in cancer populations to provide references for rational drug use in clinical practice and to promote safe and appropriate medication use in elderly cancer patients. Furthermore, we explore the role of clinical pharmacists in intervening on PIM in elderly cancer patients through several management approaches.

Methods

Literature Search Strategy

We conducted a computerized search of PubMed, CNKI, and Wanfang Data for formally published literature from database inception to April 2023. Chinese search terms included "肿瘤" (cancer), "癌症" (cancer), and "潜在不适当用药" (potentially inappropriate medication). English search terms included "tumor," "cancer," "neoplasms," "Neoplas," "Malignan," "Oncolog," "potentially

inappropriate medication," "Inappropriate Prescribing," "Inappropriate Medication," and "Inappropriate Drug Use."

Inclusion criteria: (1) Study subjects were elderly ($ $60 years) cancer patients; (2) Study design was cross-sectional or cohort; (3) Studies reported using PIM assessment tools; (4) Results included PIM prevalence, risk factors for PIM, or correlation between PIM and adverse outcomes.

Exclusion criteria: Conference papers and abstracts. A total of 44 articles were included, see Appendix Table 1 (scan the QR code on the article's first page to view).

Results

PIM Screening Tools

2.1.1 AGS Beers Criteria Most current studies have used the AGS Beers Criteria, which was initially developed in 1991 as a tool to identify potentially inappropriate medications for elderly patients based on expert consensus and extensive literature review [5,7]. The AGS Beers Criteria was the first PIM screening tool developed, and many national PIM screening tools have drawn upon its content to varying degrees [11]. It is also the most widely used screening tool in elderly cancer populations [12].

2.1.2 STOPP/START Criteria In the STOPP/START criteria, START is a comprehensive tool for determining the appropriateness of initial prescriptions, while STOPP assesses current medication use. The 2014 updated STOPP/START criteria also focused on antiplatelet and anticoagulant drugs, medications affecting renal function, and drugs with anticholinergic burden [8]. The STOPP/START criteria are also commonly used for medication review in elderly cancer patients, with greater emphasis on inappropriate medication use in the context of disease states [12].

2.1.3 Chinese Criteria for Potentially Inappropriate Medication Use in Older Adults (2017 Edition) The Chinese Criteria for Potentially Inappropriate Medication Use in Older Adults (2017 Edition) consists of two parts: Part 1 includes the Chinese PIM criteria for older adults, covering 13 categories with 72 drug types, each with 1-6 medication risk points; Part 2 includes PIM criteria for older adults under specific disease states, covering 44 drug types across 27 disease states [6].

When different criteria are applied to the same population, PIM prevalence rates differ, with poor consistency between tools [13]. TIAN et al. [13] found that the detection rate of PIM using the Chinese Criteria (34.37%) was slightly higher than that using the AGS Beers Criteria (32.65%), with only fair agreement between the two tools (Kappa=0.469, P<0.001). Another study using both

AGS Beers Criteria and Chinese Criteria to review cancer patients' medications reported PIM prevalence rates of 72.01% and 45.05%, respectively [14].

Therefore, WHITMAN et al. [15] questioned whether these tools are equally applicable to elderly cancer patients. For example, benzodiazepines used for supportive care during chemotherapy may be appropriate, yet existing criteria typically classify benzodiazepines as inappropriate medications. Similarly, first-generation antihistamine diphenhydramine is listed as potentially inappropriate, yet it is an essential component of chemotherapy premedication.

2.1.4 Geriatric Oncology-Potentially Inappropriate Medication (GO-PIM) Scale HSHIEH et al. [16] provided a new approach for reviewing medications in elderly cancer patients by converting the list of supportive care medications requiring caution in older patients from the NCCN Clinical Practice Guidelines in Oncology: Older Adult (2020.v2) into the GO-PIM scale, see Appendix Table 2 [16]. The NCCN guidelines mention medication review in the geriatric screening tool section, recommending use of AGS Beers Criteria, START/STOPP criteria, etc., to assess medication appropriateness. In the section focusing on supportive care medications, the guidelines list corticosteroids, benzodiazepines, non-benzodiazepine hypnotics, first-generation antihistamines, and other drug categories.

The GO-PIM scale offers several advantages over existing criteria: (1) It more comprehensively considers both geriatric and oncology perspectives; (2) It not only lists medications requiring caution in elderly cancer patients but also provides specific prescribing recommendations and alternative treatment options for clinicians; (3) The NCCN Clinical Practice Guidelines in Oncology: Older Adult (2020.v2) are regularly updated by oncologists and geriatricians, ensuring that relevant drugs and recommendations align with actual cancer treatment practices.

Drugs classified as potentially inappropriate in existing criteria are often appropriate in cancer treatment. Therefore, when investigating PIM prevalence in cancer patients, researchers must consider the inconsistencies between various criteria and the specific nature of cancer treatment, selecting appropriate screening tools for cancer patients. The GO-PIM scale offers physicians and pharmacists a new research approach worth learning from.

Prevalence of PIM in Elderly Cancer Patients

2.2.1 Higher PIM Prevalence in Cancer Patients Than Non-Cancer Patients PIM prevalence differs substantially between cancer and non-cancer patients, as cancer treatment and supportive care increase medication use. FENG et al. [17] found that PIM prevalence was significantly higher in colorectal and breast cancer patients than in non-cancer patients. SONG et al. [18] demonstrated that the use of multiple PIMs was more severe in cancer patients than in non-cancer patients. Additionally, PIM prevalence increases with cancer

treatment initiation; one study found that 52.9% of patients had PIM before starting cancer treatment, and 36.7% experienced worsening PIM after treatment began [19].

2.2.2 PIM Prevalence Across Different Cancer Types Surveys of PIM prevalence across different cancer types revealed: colorectal cancer patients had PIM rates of 22.5%-71.4% [17,20]; breast cancer patients had rates of 22.2%-61.7% [21-22]; lung cancer patients had rates of 28%-45% [23], with a 逐年增高 (yearly increasing) trend [24]; hematologic malignancy patients had rates of 19%-49% [25-26]. Inconsistencies between studies result from different screening tools used, with AGS Beers Criteria typically yielding higher PIM prevalence rates, as well as varying patient conditions and treatment complexity.

TIAN et al. [24] found an increasing trend in PIM prevalence among lung cancer patients, a pattern that should draw researchers' attention regarding whether it applies to other cancer types. As related research increases, investigators are shifting focus from general cancer populations to specific cancer types. These findings indicate that PIM prevalence varies across different tumor groups, with differences related not only to screening tools but also to patients' health status, cancer stage, and age. Therefore, investigating specific tumor types facilitates more targeted interventions.

Major Drug Categories Involved in PIM Among Elderly Cancer Patients

PIM in elderly cancer patients primarily involves benzodiazepines, proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, first-generation antihistamines, and metoclopramide. These medications are frequently used in elderly cancer treatment but are typically considered high-risk for older adults in PIM criteria.

2.3.1 Benzodiazepines Long-term benzodiazepine use may lead to drug dependence and serious adverse reactions. Studies have shown benzodiazepines are associated with increased risks of cognitive impairment, delirium, somnolence, traffic accidents, and fractures [27]. The NCCN Clinical Practice Guidelines in Oncology: Older Adult (2020.v2) state that benzodiazepines may be used for supportive care in elderly cancer patients during chemotherapy, with attention to dose reduction or extended dosing intervals and avoidance of abrupt discontinuation or rapid tapering. However, they are not recommended for anxiety treatment; selective serotonin reuptake inhibitors (SSRIs) may be considered, and cognitive behavioral therapy is an option for insomnia [28].

2.3.2 Proton Pump Inhibitors (PPIs) Long-term PPI use may increase risks of fractures, vitamin B12 deficiency, hypomagnesemia, and *Clostridioides difficile* infection in elderly patients [29].

2.3.3 Opioids Opioid use may increase constipation, nausea, cognitive impairment, respiratory depression, and QT interval prolongation [30]. The NCCN guidelines recommend considering non-opioid analgesics such as NSAIDs and acetaminophen whenever possible. If opioids are necessary, strict adherence to dosing instructions is required, and patients should receive bowel regimens to prevent severe constipation [28].

2.3.4 Metoclopramide Elderly cancer patients receiving low emetogenic risk chemotherapy may use metoclopramide for prophylactic antiemesis, which can cause central nervous system depression and falls, particularly in elderly, fatigued, or frail patients [31]. The NCCN guidelines recommend avoiding metoclopramide and suggest short-term corticosteroids or other antiemetics [28].

2.3.5 Diphenhydramine Diphenhydramine is unsuitable for older adults due to strong anticholinergic properties, with dose-dependent adverse effects including dry mouth, blurred vision, urinary retention, constipation, orthostatic hypotension, and tachycardia [32]. The NCCN guidelines recommend using diphenhydramine for supportive care only when definite benefit is identified [28].

Clinicians should carefully assess the risks and benefits when prescribing these commonly used drugs in elderly cancer patients. During treatment, attention should be paid to medication duration, drug-drug interactions, and close monitoring of hepatic and renal function and electrolyte levels.

Risk Factors for PIM Occurrence

2.4.1 High Medication Count, Multiple Comorbidities, and Advanced Age Literature reviews revealed that high medication count, multiple comorbidities, and advanced age are risk factors for PIM in both cancer and non-cancer patients [4,33]. When patients have polypharmacy ($ $5 medications), $ $5 comorbidities, or are aged $ $75 years [4,33], clinicians should be vigilant for PIM when prescribing.

2.4.2 Female Gender Results indicate that female patients have a higher risk of PIM than male patients [21]. This may be because elderly female patients are more susceptible to drug-related harm due to pharmacodynamic and pharmacokinetic changes [34]. ROCHON et al. [35] also emphasized the impact of gender on health, disease, and medication use, yet existing PIM screening criteria do not address gender differences, and most studies have not analyzed PIM effects by gender.

2.4.3 Cancer Treatment Modalities Cancer treatment modalities are also risk factors for PIM in elderly patients [14,17]. FENG et al. [17] found that receiving chemotherapy (vs. none) was associated with PIM in breast and colorectal cancer patients. Additionally, colorectal cancer patients had increased PIM

risk after radiotherapy, related to post-radiation condition changes. A domestic study similarly found that elderly cancer patients receiving anticancer drug therapy (vs. surgery or radiotherapy) had higher PIM risk, related to greater anticancer drug toxicity and need for premedication and other interventions [14].

2.4.4 Cancer Type and Quality of Life Impact TIAN et al. [13] found that among all cancer types, only lung cancer was associated with PIM occurrence, with higher PIM prevalence related to poorer physical and mental status and treatment toxicity. ALKAN et al. [36] found that poor Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scores may be significantly associated with PIM. ECOG-PS reflects cancer patients' quality of life, with scores of 3-4 indicating poor quality of life and inability to live completely independently.

Given substantial differences in included patients across studies, current results are inconsistent. Future research should emphasize adjustment for comorbidities and focus on specific cancer types to make findings more representative. Currently, no such studies exist domestically, while foreign research has demonstrated associations between PIM use and increased mortality in elderly cancer patients, highlighting the need to examine correlations between PIM and adverse prognosis in this population.

Relationship Between PIM and Adverse Outcomes

2.5.1 Increased Mortality Risk A meta-analysis by CHEN et al. [2] showed that PIM was statistically significantly associated with all-cause mortality in elderly cancer patients, with a 43% increased mortality risk among those with PIM [RR=1.43, 95%CI (1.08, 1.88)]. However, PIM showed no statistically significant association with hospital readmission rates, prolonged hospital stays, or treatment-related toxicity. The meta-analysis had limitations, including failure to control for the confounder of indication. Drug indication is a potential confounding factor, so models should be adjusted for comorbidities. Additionally, treatment adherence was not controlled; when healthier patients tend to adhere to treatment while more severely ill patients tend not to receive or adhere to treatment, study results can be biased [37].

A subsequent Danish study demonstrated that PIM use was significantly associated with mortality in elderly cancer patients, with HR values of 1.50 for patients with 1-2 PIMs and 2.38 for patients with $ $3 PIMs at 6-12 months post-diagnosis [38].

2.5.2 Increased Drug Interaction Risk A cohort study by RAMSDALE et al. [39] found PIM was significantly associated with drug interactions [OR=3.19, 95%CI (2.30, 4.42)]. Nearly 70% of patients in this cohort had risk for drug-drug interactions, with approximately 1/4 exposed to potential interactions where adverse event risk exceeded benefit. A US study found

that drug-chemotherapy interaction rates were significantly increased in elderly cancer patients with PIM. In colorectal cancer, the most common potential interactions were capecitabine with hydrochlorothiazide (22%) and warfarin (15%); in breast cancer, cyclophosphamide with hydrochlorothiazide (31%) and methotrexate with NSAIDs (16%); in lung cancer, warfarin with etoposide (14%) and gemcitabine (15%) [40].

2.5.3 Increased Adverse Event Risk HSHIEH et al. [16] used the GO-PIM scale for medication review and found PIM was associated with frailty among elderly blood cancer patients. Other studies have shown PIM is associated with balance problems, syncope, and impaired health in elderly cancer patients [26,41]. Since PIM can lead to mortality, drug interactions, readmissions, and other adverse events, it may increase healthcare costs. A study of elderly patients with breast, prostate, and colorectal cancers found PIM use was positively correlated with non-drug costs and total medical expenses for these three cancer types [22].

In summary, when patients have high medication counts, multiple comorbidities, and advanced age, clinicians should be more cautious with prescribing. Although research on gender effects is limited, existing evidence suggests female patients may be more susceptible to drug-related harm, warranting close monitoring during treatment. For cancer patients, the risks of PIM associated with cancer itself and cancer treatment modalities should also be considered, prompting careful assessment of medication risks and benefits in clinical practice to reduce unnecessary drug use and promote rational medication use in elderly cancer patients.

Role of Clinical Pharmacists in PIM Management

Clinical pharmacists are essential members of the multidisciplinary team (MDT) [42], and their interventions in cancer patient care help identify drug-drug interactions, drug-induced adverse reactions, ensure treatment appropriateness, provide cost-effective recommendations, and improve medication adherence [43]. The pharmaceutical care process for cancer patients primarily includes medication reconciliation, assessment of drug-related problems (DRPs), and implementation and follow-up of medication optimization recommendations [42]. Medication reconciliation involves comprehensive collection of patients' medication history, adverse reaction history, and drug allergy information, followed by assessment of whether prescriptions contain DRPs using screening tools combined with patient information. After consultation with patients and clinicians, medications are optimized through changes, deprescribing, or adding over-the-counter drugs.

Clinical pharmacists' interventions require comprehensive patient assessment and communication with clinicians, so identifying high-risk patients with DRPs can improve efficiency. A domestic study developed a PIM risk prediction model for outpatient lung cancer patients, which defines PIM risk levels based on

the presence of related risk factors [44] and can assist pharmacists in deciding which patients require intervention. However, a comprehensive risk prediction model applicable to all cancer patients remains to be developed. Currently, the AGS Beers Criteria remain the primary PIM screening tool for elderly cancer patients, yet for some cancer patients, the clinical benefits of drugs classified as PIM may outweigh potential risks. This requires clinical pharmacists to make comprehensive judgments based on clinical knowledge and patient conditions, and participation in developing cancer-specific PIM screening tools is crucial.

Summary and Outlook

Identifying PIM in elderly patients helps prevent and reduce drug-related adverse events and promotes safe and rational medication use. The AGS Beers Criteria are most commonly used for medication review in elderly cancer patients, with high PIM prevalence rates. Major drug categories include benzodiazepines, NSAIDs, and PPIs. Polypharmacy, comorbidities, and age are common risk factors for PIM in elderly patients, while treatment modalities and cancer types are also important factors in cancer patients.

Due to limited current research, relationships between PIM and adverse outcomes such as mortality, overall survival, readmission rates, drug interactions, and adverse event rates show inconsistencies. Future research should more deeply explore PIM's impact on various adverse outcomes in cancer patients, with studies targeting different cancer types. Additionally, clinical pharmacists can effectively ensure medication appropriateness and safety in elderly cancer patients through comprehensive medication review, playing a significant role in patient care. Current research demonstrates that PIM is highly prevalent among elderly cancer patients. As PIM in this population gains increasing attention, related prescribing screening tools and management methods will continue to improve.

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Conflict of Interest: The authors declare no conflicts of interest.

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